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PRIMARY VIRUS PNEUMONITIS

A COMPARATIVE STUDY OF TWO EPIDEMICS

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DURING the winter months of 1940-1941, there occurred in Minnesota an epidemic of acute pneumonitis among infants which was similar in all respects to that previously described by one of us (J. M. A.[1]). Clinical and pathologic data from the second epidemic are now available for comparison with those recorded in connection with the earlier one. Some progress has been made in the biologic study of the etiologic virus since the previous report was presented. Growing interest in the general subject of acute pneumonitis is evident from the rapidly increasing number of reports in the literature[2-5] and from personal communications[6, 7] from various regions of the United States.

Description.—The form of acute primary pneumonitis under consideration here is characterized by its predilection for young infants, its epidemic nature, its high degree of contagiousness, and the constancy of the symptom pattern. Cough, dyspnea, cyanosis, and low-grade fever are the most outstanding clinical features. Elevation of body temperature has not exceeded 102.5° F. in 75 per cent of the cases observed. Widely scattered, fine râles are the only characteristic auscultatory findings from examination of the chest. However, roentgenograms of the lungs have shown patchy densities suggestive of bronchopneumonia in nearly all cases. Typical cytoplasmic inclusion bodies are demonstrable in the epithelial cells of the bronchial tree in fatal cases. The mortality was 28 per cent in the first epidemic, 14 per cent in the second, and 20 per cent in the two epidemics combined.

Symptoms, Signs, and Mortality.—A correlation of symptoms, signs, and mortality in the two epidemics is shown in Fig. 1.* This shows

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*Dichotomous table prepared by Dr. Edith Boyd.

that 62 per cent of the infants had all of the three cardinal symptoms: cough, dyspnea, and cyanosis. Of this group, 35 per cent had temperatures reaching the range between 102.6° F. and 105° F. at one time or another during their course; 65 per cent had temperatures in the moderate range, 99.8° F. to 102.5° F. A further analysis of Fig. 1 shows that 56 per cent of the infants with cough, dyspnea, cyanosis, and high body temperatures died, while only 20 per cent of those in the same symptom group, but with moderate temperatures, succumbed. Only patients with cough, dyspnea, and cyanosis died.

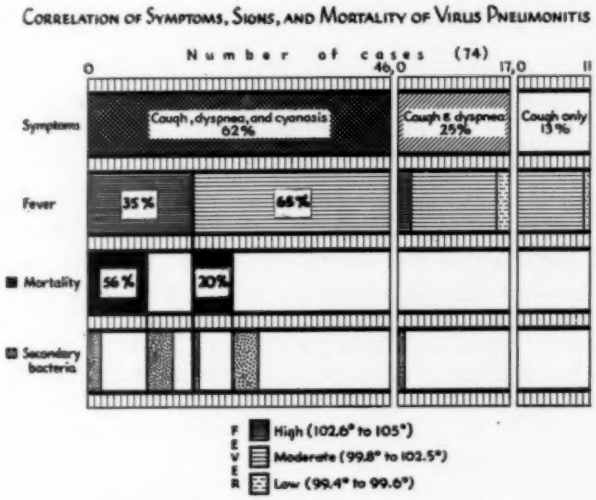

Fig. 1.—Diagrammatic chart of clinical features.

The lowest bar in Fig. 1 shows the number of patients with "secondary bacterial invasion." This includes those in whom a specific type of pneumococcus was found during life or in whom a significant bacterial agent was recovered from the lungs at necropsy. In two cases, staphylococcus empyema was found post mortem. Only one patient with a type-specific pneumococcus infection (type XXVII) died. In 25 per cent of the fatal cases was a secondary bacterial agent found to be of significance.

Age Incidence.—In Fig. 2 the correlation of symptoms, signs, mortality rate, age incidence, and time of onset of the disease is shown for both full-term and premature infants. The age of greatest susceptibility is indicated by the sixteen cases in which the onset of the disease began in the *fourth* week of life. The high incidence of susceptibility from the twenty-first to the fifty-sixth day of life as well as the remarkably low incidence in the neonatal period is shown in the figure. No relationship

of postnatal age to severity of symptoms or mortality could be deduced. Deaths were fairly evenly distributed through all ages from 2 to 15 weeks. The high mortality rate (83 per cent) among the premature infants is notable, but a high percentage of these deaths occurred after the fourth week of life, a time when the mortality from prematurity per se is very low. The mortality rate among the full-term infants was 8 per cent. The onset of the disease was recorded in only one case prior to the fourteenth day of life.

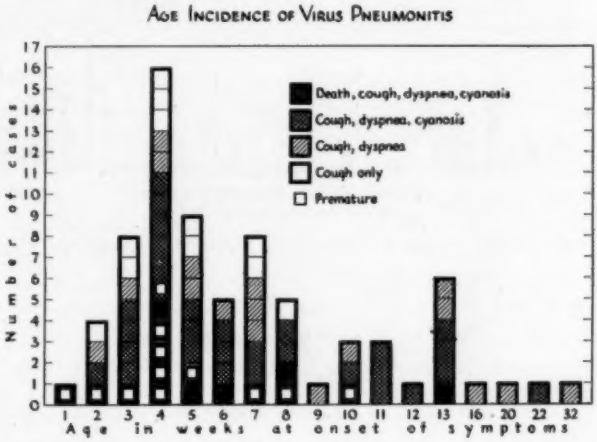

Fig. 2.—Diagrammatic chart of age incidence correlated with clinical features and mortality.

Epidemiology.—Fig. 3 indicates the day of the month when each patient became ill. The epidemic character of the disease is suggested by the grouping of cases at weekly intervals. As in the first epidemic, the initial cases occurring during the second were discovered at the University Hospital. Frequent transfers from the University Hospital to the Booth Memorial Hospital probably provided the means of spread in both epidemics. The first cases to appear at the Booth Memorial Hospital were infants who had been transferred from the University Hospital at the end of the neonatal period. In the epidemic of February, 1937, every infant in the Booth Memorial Hospital became ill. In the 1940 epidemic during November and December, every infant there, with the exception of one, became ill. In a recrudescence of the second epidemic in March, 1941, the contagiousness of the disease was not nearly so great, nor were its manifestations so severe as in the previous outbreaks. In spite of this variation, the disease must be regarded as being highly contagious for young infants. No adults coming into contact with sick infants became ill.

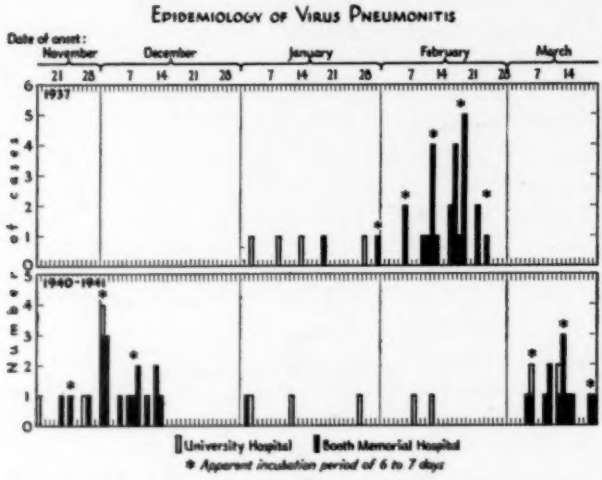

Fig. 3.—Epidemiology of the disease, represented diagrammatically.

TABLE I

COMPARISON OF 1937 AND 1940-1941 EPIDEMICS

	1937		1940-1941	
		DEATHS		DEATHS
Total cases	32	9	42	6
Mortality	28%		14%	
Cough	32 (100%)		42 (100%)	
Dyspnea	30 (93%)		33 (78%)	
Cyanosis	20 (62%)		26 (62%)	
Average highest temperature	101.5° F.		101.1° F.	
Average highest W.B.C.	19,140, 48% P.M.N.		13,500, 47% P.M.N.	
Specific pneumococci	Type XXIII, 4	0	Type XIX, 2	0
	Type XXVII, 3	1	Type XVIII, 1	0
Complications	Otitis media, 5	1	Otitis media, 4	1
	Empyema, 1	1	Empyema, 1	1
			Lung abscesses, 1	1
			Diarrhea, 4	2
Treatment	Chemotherapy, 0		Sulfathiazole, 8	1
			Sulfapyridine, 4	2
			Sulfanilamide, 1	1
	Transfusions, 5	2	Transfusions, 13	4
	Blood subcutaneously, 1	1	Blood subcutaneously, 7	0
	Blood prophylactically, 0		Blood prophylactically, 7	0*

*Five of these seven infants subsequently developed pneumonitis with no deaths.

Comparison of Epidemics I and II.—In Table I the various features of the two epidemics are listed for comparison. An outstanding difference between the two outbreaks was the more widespread nature of the second. Many of the private hospitals in Minneapolis experienced mild epidemics of short duration during the time of the 1940-1941 epidemic. Pathologic specimens of lungs collected from some of these cases showed the same features as those observed in the University Hospital and Booth Memorial Hospital cases. As indicated by the clinical course, the disease was definitely milder in the 1940-1941 epidemic than in the 1937 epidemic, and the mortality rate was just half as great. The average age of the infants at onset of symptoms was slightly over 7 weeks in both epidemics. The symptoms were almost identical in the two series. The course was prolonged with persistent coughing and low-grade fever.

No significant bacteriologic agents were disclosed in either epidemic. The findings are listed in Table I. Only 17 per cent of the eighteen cases from the University of Minnesota Hospital included in the recent study had a type-specific pneumococcus by culture, whereas 65 per cent of infants treated simultaneously at the same institution for other forms of pneumonia showed type-specific pneumococci. The complications were the same in the 1937 and the 1940-1941 epidemics except for a few cases of diarrhea in the more recent outbreak, a symptom which was absent in the first. Diarrhea was probably directly responsible for death in two of the more recent cases.

In the first epidemic, all fatalities, with the exception of one, occurred within the first week of illness, the primary cause of death being the pneumonitis. In the second epidemic, four patients died of complications from nineteen to forty days after the onset of the pneumonitis. The remaining two fatalities occurred within one week. Further comments on this feature are made in the discussion of the pathology of the disease.

Roentgenologic Findings.—Roentgen ray studies in eighteen cases at the University Hospital demonstrated positive findings in fifteen. These were described as fine patchy densities, involving the right and left upper lobes in over 90 per cent of the positive cases. The four films shown in Fig. 4 are from different babies and reveal the usual changes. Pathologic studies suggest that the findings by x-ray are probably related to capillary bronchiolitis and scattered secondary atelectasis. Resolution of the pneumonic process, as determined by roentgenograms, was slow in the majority of cases. Changes persisted after clinical recovery in many patients.

Pathology.—In the original paper[1] the gross and microscopic changes observed in nine fatal cases were reported. The prominent pathologic features were proliferation and sloughing of bronchial epithelium. The exudate in the bronchial lumen was primarily epithelial in character, and the principal infiltrating cell in the peribronchial areas and the parenchyma was mononuclear. Atelectasis, edema, and hemorrhage

were noted. Cytoplasmic inclusion bodies were found in the diseased epithelial structures of the lung. These bodies varied from 3 to 6 μ in diameter, stained acidophilic with the hematoxylin and eosin and also with the Giemsa stain, were often surrounded by a clear halo, and in a few instances contained vacuoles.

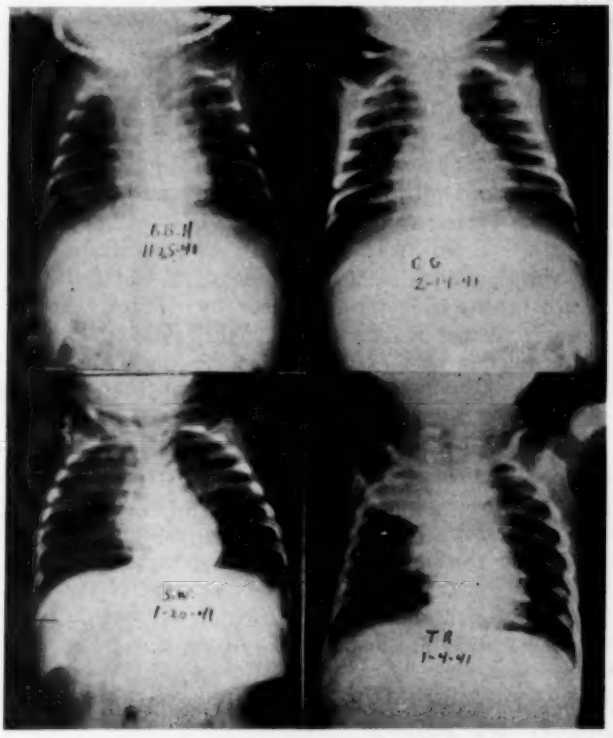

Fig. 4.—Chests of four infants, showing typical changes interpreted as patchy bronchopneumonia. The chest in the lower right shows atelectasis of the right upper lobe.

In the 1940-1941 epidemic, six deaths were directly or indirectly related to the pneumonitis. One patient recovered clinically from the disease but died at home a few days following discharge. Unfortunately no details regarding the nature of the terminal illness could be obtained. In the five remaining fatalities, autopsies were performed. One of the latter infants died one month after the onset of pneumonitis. He had recovered from the acute phase of this disorder, but developed diarrhea and died within a few hours. At autopsy, his lungs showed no remaining evidences of pneumonitis. Two additional infants survived the initial stages of the pneumonitis but died subsequently of staphylococcus pneumonia, positive blood cultures being recorded in each instance. The lung findings were those of staphylococcus pneumonia with

multiple abscesses and empyema. The remaining two infants died in the acute phase of pneumonitis within seven days of the onset of the

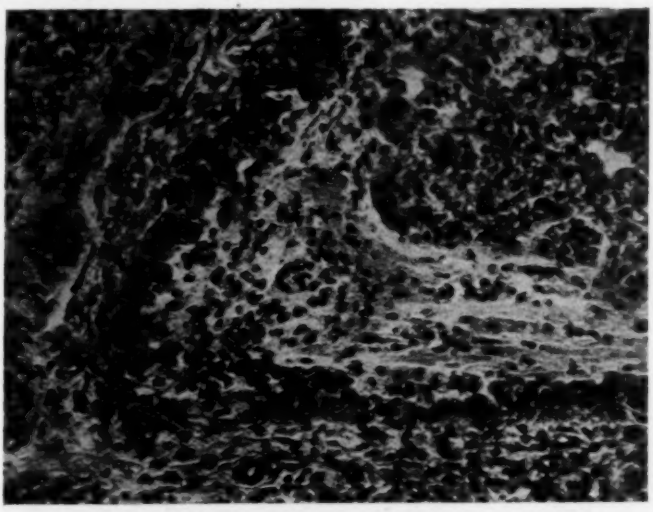

Fig. 5.—Section showing proliferation and sloughing of epithelium with hyaline-like material in the lumen of the bronchiole. (Photomicrographs were made by H. M. Morris, M.P.A.)

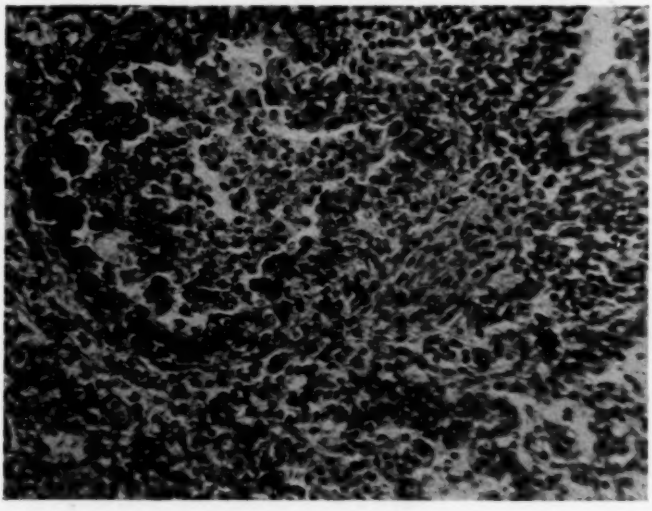

Fig. 6.—Section showing proliferation and sloughing of epithelium with peribronchiolar infiltration of mononuclear cells.

disease. In each of these the typical lung changes were seen, including inclusion bodies in the diseased epithelial structures. These changes are

shown in Figs. 5-8. The microscopic sections of lungs from a patient dying in another hospital at the time of the recent epidemic were made available to us and the same changes were observed (Figs. 9 and 10).

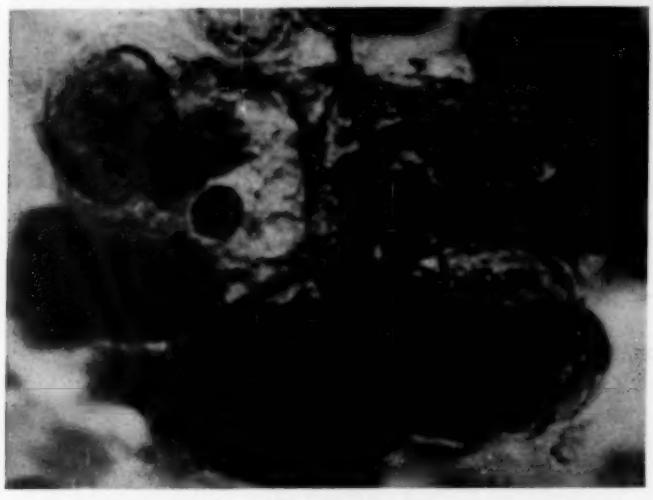

Fig. 7.—Section showing cytoplasmic inclusion bodies in bronchial epithelium. Note small vacuoles in the body on the left and halo about the body. Arrows indicate other bodies not clearly in focus. Stain is hematoxylin and eosin.

Fig. 8.—Section stained with Giemsa showing two inclusion bodies. Cellular detail and nuclei are not shown clearly with this stain, but inclusion bodies stain bright red or acidophilic.

Pathology of Control Cases.—Microscopic sections of the lungs of twenty infants who died as a result of other respiratory infections were

searched for cytoplasmic inclusion bodies. These control cases ranged in age from a few weeks to 7 months. The most common pathologic diagnosis was bronchopneumonia. Other diagnoses were tracheobronchitis, interstitial pneumonia, hemorrhagic pneumonia, and one case of lobar pneumonia, type XIV. No inclusions were seen in any of these cases.

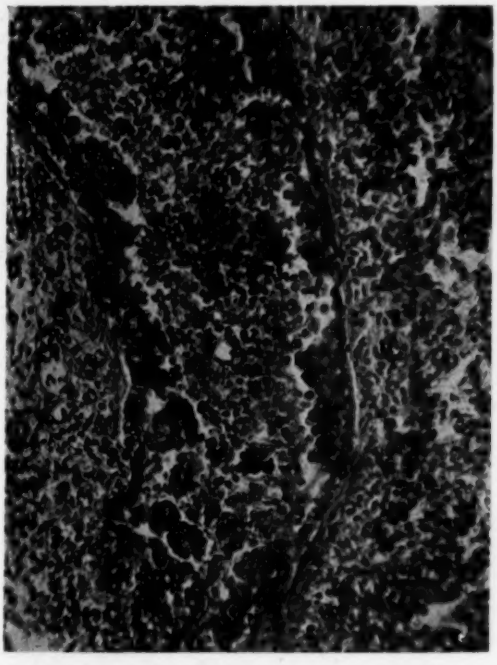

Fig. 9.—Section showing proliferation and sloughing of epithelial cells, monocytic exudate, and atelectasis from a case outside the present epidemic (St. Mary's Hospital).

Differential Diagnosis.—This phase of the subject was discussed with reference to similar virus diseases in the original publication[1] and, therefore, will not be elaborated here. All forms of acute pulmonary disease in infants must be eliminated, chiefly by bacteriologic studies of the sputum. Staphylococcus pneumonia in the infant may simulate primary pneumonitis very closely in certain respects. Failure to identify an etiologic agent of an epidemic disease in infants having the symptomatology set forth here should lead the physician to suspect a virus as the most likely cause of the illness.

Cytoplasmic Inclusion Bodies in Throat Smears.—At the onset of the 1940-1941 epidemic, smears were made of the secretions and exudates in the throats of infants suffering from pneumonitis to determine the presence of inclusion bodies. These smears contained chiefly epithelial cells,

very few pus cells and bacteria being present. A high percentage of these infants showed cytoplasmic inclusion bodies in the epithelial cells. With the hematoxylin and eosin stain some of these bodies appeared to stain basophilic, but predominantly they were acidophilic. Sizes varied from 2 to 8 μ in diameter (Table II and Figs. 11 and 12). What significance can be attached to this finding we are not prepared to state as yet. Finding a much higher percentage of strongly positive smears in the sick infants than in normal control infants has led to further studies, which are now in progress.

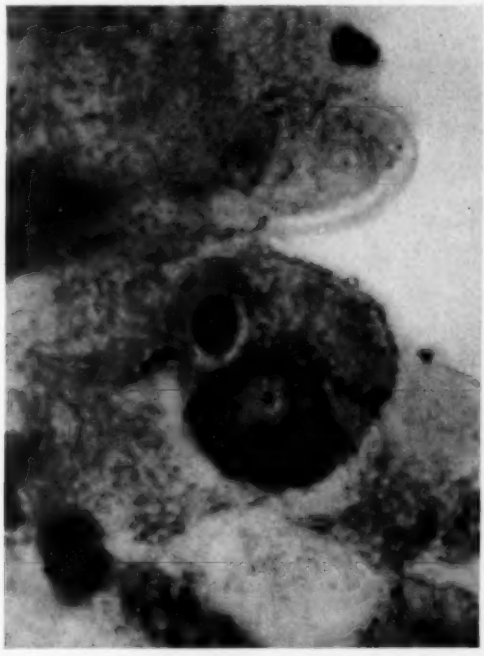

Fig. 10.—Section showing cytoplasmic inclusion body from the same patient as in Fig. 9. Note halo and indentation of nucleus. Stain is hematoxylin and eosin.

Throat smears from nineteen adults who were in close contact with the mothers and sick infants were examined for inclusion bodies. A very low incidence of positive cells was disclosed. Inclusion bodies were found in the throat smears of two of the nurses, both with histories of recent upper respiratory infections. Similarly appearing inclusion bodies have been demonstrated by Broadhurst and her associates[8] to be present in throat smears of young adults suffering from mild respiratory infections.

During August, 1941, when no infections were present at the Booth Memorial Hospital, smears from eighteen infants were examined and in

no instance were cells found to contain inclusion bodies. In October, 1941, ten additional infants were examined, one case only being positive. Contrasted with these findings are those recorded of the infants ill with pneumonitis in the past epidemic. Eighty-five per cent of the latter were positive for cytoplasmic inclusions (Table II). In the four negative cases only a single slide was available for study. All four were cases occurring after the peak of the epidemic. One of these infants died of staphylococcus pneumonia and no inclusions were found in the pathologic sections. Four of thirty-three control infants at the University Hospital were found to have cytoplasmic inclusions in their pharyngeal smears in August and October, 1941. We wish to emphasize that the full significance of the finding of many inclusion bodies in the pharyngeal smears of patients with pneumonitis is not yet apparent. Further study is warranted, however, to determine its possible value in the clinical diagnosis of virus pneumonitis.

TABLE II

RESULTS OF THROAT SMEAR EXAMINATIONS FOR THE PRESENCE OF INCLUSION BODIES

SUBJECTS	NUMBER OF CASES	2 OR MORE POSITIVE PER 100 CELLS	6 OR MORE POSITIVE PER 100 CELLS	12 OR MORE POSITIVE PER 100 CELLS	18 OR MORE POSITIVE PER 100 CELLS
Infants with pneumonitis	28	24 (85.7%)	22 (78%)	17 (60%)	15 (53%)
Adults exposed, not ill; history of recent upper respiratory infection	19	2 (10%)	1 (5%)	0	0
Well babies, August, 1941	18	0	0	0	0
Well babies, October, 1941	10	1 (10%)	0	0	0
Infants not ill with pneumonitis, August, 1941	23	3 (13%)	3 (13%)	0	0
Infants not ill with pneumonitis, October, 1941	10	1 (10%)	0	0	0

Biologic Studies.—Although rather extensive attempts have been made to establish an infection in experimental animals and chick embryo tissues, no conclusive results have as yet been attained. Glycerinated and frozen lung tissues from acute cases resulting fatally and having large numbers of typical inclusion bodies in the bronchial epithelium have been the major source of material. Inoculations were made intracranially, intraperitoneally, and intranasally. The technique recently described by Burnet[9] for use with pneumotropic viruses was employed in the chick embryo experiments.

An attempt was made to adapt the virus to Swiss mice. Inoculating three mice with original material, six serial transmissions were carried

out, using three mice for each transmission. Into each series of mice an injection of the original source material was also made. Animals were

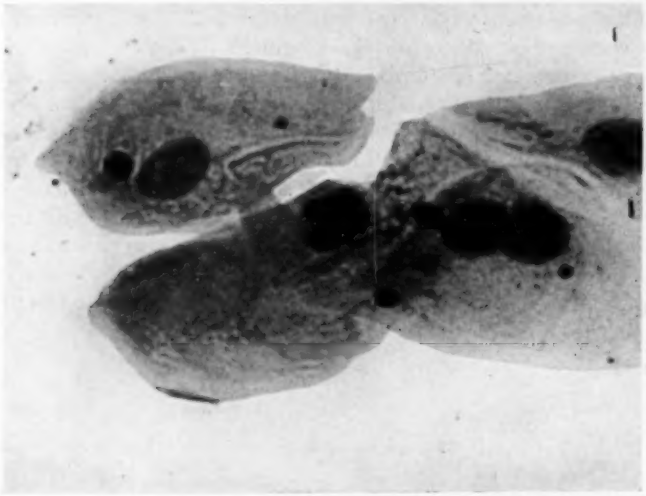

Fig. 11.—Throat smear showing epithelial cells with cytoplasmic inclusion bodies. Note halo about body on the left. Stain is hematoxylin and eosin.

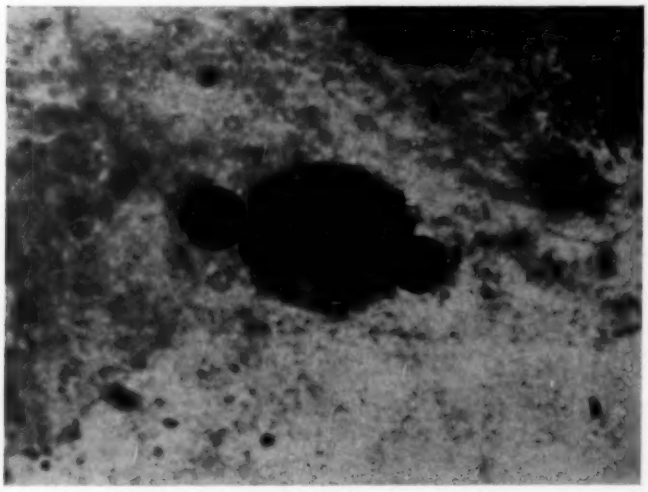

Fig. 12.—Throat smear showing epithelial cell (oil immersion) with two inclusion bodies. Note halo and indentation of nucleus. Stain is hematoxylin and eosin.

killed from three to eight days after inoculation. Nodular lesions discovered in some of the mice after the fourth series appeared to represent a bacterial rather than a virus infection. Microscopic study failed to

show the typical inclusion bodies or other evidence of a virus infection observed in infants.

Field mice were inoculated intranasally, and serial passages were carried out without significant positive results. As a further test, a group of ten field mice were inoculated intranasally. Five were kept at 37° C. in an incubator, and five were held at room temperature. All remained well, and their lungs were found to be normal. It was concluded that the virus of infant pneumonitis could not be established in field mice.

An attempt was made to transmit the disease to ferrets. In the first experiment two ferrets were inoculated intracranially, intraperitoneally, and intranasally with a suspension of frozen lung tissue. One died on the fifth day with a brain abscess; the other had a temperature of 104.5° F. on the second day after inoculation. The temperature remained variable but lower than 104.5° F. for twelve days, following which the ferret continued well. Two additional ferrets were inoculated intranasally and intraperitoneally with a suspension of both glycerinated and frozen human lung tissue. Some slight elevations of temperature were observed. An attempt was then made to adapt the disease to ferrets by serial passage. Two ferrets were inoculated with a glycerinated and frozen lung suspension by cisterna puncture and by intranasal inoculation. These ferrets were killed on the fourth day, and a suspension of their lung and brain tissue was inoculated intranasally and cisternally, respectively, into each of two more ferrets. In this manner transmission was attempted through seven successive series of ferrets. In the last series one ferret was killed on the fifth day for study, one on the tenth day, and one remained well for an extended period. Ferrets in this series failed to show any consistent elevation of temperature, and the microscopic examination of lungs did not reveal evidence of a virus infection.

Ten big brown bats that were stored in hibernation under refrigeration temperatures were inoculated intraperitoneally and intranasally with a suspension of glycerinated and frozen lung. After inoculation they were kept at room temperature and all remained alive and apparently well for more than two weeks. No significant symptoms or objective changes were observed which would indicate establishment of a specific disease from the inoculation.

Two guinea pigs were inoculated intraperitoneally with frozen lung tissue and six more were inoculated intraperitoneally and intranasally. All guinea pigs remained well, and examination at intervals failed to show any scrotal involvement. After extended observation, guinea pig inoculations appeared to rule out appearance of rickettsial disease and to establish that the infant pneumonitis could not be produced in guinea pigs.

A single short-tailed shrew died eight days after intranasal inoculation, showing a bronchial pneumonia with small bodies, which appeared to be inclusion bodies in bronchial epithelium. Additional shrews could

not be obtained for further experimentation. Entirely negative results were obtained from the inoculation of three deer mice, two bog lemmings, three weasels, two young rabbits, two suckling dogs, and four suckling cats.

A suspension of lung was inoculated through the chorioallantois into the amniotic fluid of chick embryos. Serial passage at three- to seven-day intervals was carried through seven generations. Embryos were not killed by the virus, and no lesions recognizable grossly were observed. Histologic study of embryos from the first and seventh generations, like the controls, were all negative. Mammalian fetal inoculation experiments are now in progress.

Treatment.—The usual supportive measures employed in the management of any infant ill with pulmonary disease proved to be of value except for too liberal use of parenteral fluids. It was repeatedly observed that infants suffering from acute primary pneumonitis tolerated parenteral fluids very poorly. Liquids offered by mouth were usually taken reluctantly or were refused. Frequently when parenteral fluids were administered, the three most severe signs of this form of pneumonitis, cough, dyspnea, and cyanosis, appeared to become accentuated.

Oxygen was the most valuable therapeutic agent employed. Postural drainage, maintained by lowering the head of the crib, and gentle aspiration of the nose and throat by means of a soft-rubber-tipped syringe were frequently used. The humidity in the ward was maintained by use of steam. The various sulfonamide drugs available were employed. While their influence on secondary bacterial invasion undoubtedly lowered the mortality rate, their effects on the primary disease were equivocal. Blood transfusions were given in thirteen of the most seriously sick infants. Four of these subsequently died. Thirty cubic centimeters of whole adult blood were given to seven babies in the very early stages of the disease; no deaths occurred in this small group. Seven additional infants exposed in the ward were also given 30 c.c. of whole adult blood, and, although five of these subsequently developed pneumonitis, no deaths resulted.

In summary, management included continuous administration of oxygen, maintenance of a humid environment, drainage and aspiration of the posterior pharynx, whole blood transfusions, chemotherapy, and parenteral fluids, the latter, however, only if specifically indicated. In a personal communication to us, Dr. C. A. Aldrich stated, "We have seen apparently favorable results from the use of suprarenal cortical extract (Upjohn) in cyanotic infants, particularly in premature and very young babies." We have not as yet had any experience with this form of therapy.

COMMENTS

Young and premature infants appear to be the most susceptible hosts of the pneumotropic virus with which we are dealing. The age incidence

curve indicates relative immunity during the first 10 days to 2 weeks of life. In our series of cases the peak of infectivity was shown to be in the fourth and fifth weeks of life. Adults in both epidemics manifested immunity which was apparently complete. Such universal immunity on the part of adults would suggest that the virus involved is widespread in nature but causes clinically recognizable disease in the susceptible infant host only.

All twelve premature infants in the epidemics exposed to this disease became profoundly ill and ten of them died. The average age at onset of the pneumonitis was 34 days, suggesting the presence of some factor of susceptibility other than ordinary physical immaturity per se. The only patient to develop virus pneumonitis prior to the fourteenth day of life was a premature infant. One sporadic case of typical pneumonitis occurred in a 6-month-old infant who weighed less than 3 pounds at birth. Complete host immunity to this form of pneumonitis, as exhibited by adults, appeared quite absent in the premature infants. In comparison with prematurely born infants, full-term infants manifested a somewhat increased resistance to this infection. These clinical observations are consistent with the findings of Woolpert and co-workers[10] and of Dettwiler and co-workers[11] on the comparative susceptibility of fetal and postnatal guinea pigs to the virus of epidemic influenza. They conclude "First, that there is a gradually increasing resistance to infection with this virus during intrauterine development with but little change thereafter; and second, that at the time of birth there is a sudden loss of infectibility by routes other than the intranasal." Since prematurely born infants appear to be most highly susceptible to this form of pneumonitis in the early weeks or months of life, it is probable that resistance to infection with this virus is increased during the last few weeks of pregnancy.

SUMMARY AND CONCLUSIONS

1. Seventy-four infants with acute primary pneumonitis, occurring in two epidemics, manifested a constant symptom pattern characterized by cough, dyspnea, cyanosis, and low-grade fever. The mortality was 20 per cent. Uniform pathologic changes were found in the lungs from fatal cases. The characteristic features were as follows: (1) occurrence of cytoplasmic inclusion bodies in the epithelial cells; (2) sloughing and proliferation of bronchial epithelium; (3) accumulation of mononuclear exudate; and (4) patchy atelectasis.

2. Twenty control cases of pneumonia in infants caused by ordinary bacteria failed to show the pathologic changes typical of virus pneumonitis, and no inclusion bodies were seen.

3. Throat smears from infants with pneumonitis were compared with those from adults and infants not ill with pneumonitis as regards the presence or absence of inclusion bodies. Eighty-five per cent of the sick

infants showed positive smears, whereas less than 10 per cent of infants and adults in five control groups showed inclusion bodies.

4. Fairly extensive biologic studies on the nature of the etiologic virus have been carried out, but these have so far failed to isolate the agent.

5. The prematurely born infant is the most susceptible human host of the disease. The demonstrated susceptibility of all young infants after the neonatal period strongly contraindicates institutional care for well babies beyond this period whenever the disease is prevalent.

6. No specific therapy has as yet been developed for this form of primary virus pneumonitis. General measures, such as the administration of oxygen, postural drainage, aspiration of exudate, blood transfusion, and therapy with the sulfonamide drugs (to combat secondary bacterial infections), have appeared to be efficacious in some cases. Whole adult blood may have prophylactic value, especially in the premature infant.

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THE USE OF SULFONAMIDES IN THE TREATMENT OF SYPHILITIC KERATITIS

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INTERSTITIAL keratitis is the commonest lesion of late congenital syphilis, and it was once considered to be one of the most resistant to treatment of all syphilitic lesions. However, although many cases are resistant and recurrences are frequent, modern efficient antisyphilitic treatment usually causes improvement within two to six months.

TABLE I

SULFONAMIDES IN THE TREATMENT OF INTERSTITIAL KERATITIS

AGE* (YR.)	RACE	SEX	DURATION OF SYMPTOMS BEFORE TREATMENT (MONTHS)	DOSAGE OF DRUG† (GM.)	DURATION (DAYS)	COMMENT
13	C	F	2	0.3 t.i.d.	14	Both corneas entirely clear at end of two weeks; has had no recurrence
6	C	F	4	0.3 t.i.d.	21	Photophobia disappeared at end of first week and clouding disappeared at end of four weeks with minimal scarring; no recurrence
10	C	F	5	0.3 t.i.d.	14	Photophobia absent at end of fourteen days; corneas clear, except for scarring at end of twenty-one days; no recurrence
9	W	F	2	0.3 t.i.d.	21	Photophobia absent in seven days; eyes entirely clear in twenty-one days; no recurrence
10	C	M	1	0.3 t.i.d.	7	Photophobia cleared at end of one week; did not return for further treatment
5	C	M	-	0.25 t.i.d.	14	Photophobia absent in four days; both corneas clear at end of two weeks; no recurrence; patient was receiving antiluetic treatment
6	W	F	1	0.25 q.4.h.	14	Remarkable clearing of photophobia in one week and of clouding in two weeks

*Verbal reports have been received that this form of therapy is not as efficacious in older children or adults.

†The first five children received sulfanilamide, the sixth patient was given sulfapyridine, and the last received sulfathiazole.

Sandler[1] in 1939 reported the case of a 28-year-old white man with relapsing interstitial keratitis, which was not improving in spite of active antisyphilitic treatment along with the administration of foreign pro-

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teins and fever therapy. However, when he gave the patient 5 c.c. of prontosil and 0.56 Gm. (10 gr.) of sulfanilamide t.i.d., all symptoms subsided in ninety-six hours.

During the past two years we have treated seven children with bilateral interstitial keratitis, only one of whom had had previous antisyphilitic treatment. Five children received sulfanilamide, one sulfapyridine, and one sulfathiazole (see Table I). At the same time, antisyphilitic

Fig. 1.—*A*, Severe photophobia when treatment was instituted. *B*, Marked improvement after one week of sulfathiazole.

treatment was instituted. The clearing up of the photophobia and clouding of the cornea in periods of one to three weeks was remarkable. This could be due only to the action of the sulfonamides, since antisyphilitic therapy consisted of one or two doses of intramuscular bismuth. The child treated with sulfathiazole had such severe photophobia and lacrimation before treatment that he would not open his eyes unless he was compelled to do so by his mother. Yet in a week's time these distressing symptoms had disappeared entirely (Fig. 1).

The effect of the local application of the sulfonamides to the involved eyes has not as yet been tried, but we plan to use this method on our next patients.

Considering all available evidence as to the pathogensis of interstitial keratitis, there is nothing that would substantiate the use of sulfonamides in the treatment of this condition. Campbell[2] studied the chemotherapeutic effects of sulfanilamide and neoprontosil upon the course of experimental rabbit syphilis. In no instance was the evolution of the disease altered by therapy, and the drugs had no effect upon the motility of *Spirochaeta pallida* in vitro. Buttle[3] found sulfanilamide to be ineffective in the treatment of *Trypanosoma equiperdum* infections in mice.

This report is made with the hope that it will stimulate further controlled studies of the use of sulfonamides in the treatment of syphilitic interstitial keratitis. The results obtained in seven consecutive cases were so rapid and clear-cut that one would be justified in using the sulfonamides, at least for a short period of time, in conjunction with antisyphilitic therapy.

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STUDIES OF THE PHYSICAL CHARACTERISTICS OF CHILDREN IN MARSEILLES, FRANCE, IN 1941

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IN CONNECTION with a survey of the nutritional status of a sample of the population of Marseilles, France, conducted during the first six months of 1941, an opportunity was afforded to obtain anthropometric and other developmental data from the group of children under study. The 79 families enrolled for this survey had been chosen in such manner as to make the group as representative as possible of the population of the entire city, but the group was probably somewhat weighted on the side of low economic status. This report deals with 132 boys and 128 girls under 10 years, 3 months of age, recruited primarily from this family series but augmented by children enrolled through selected schools. These children are described in respect to body measurements, certain clinical attributes, and the observations made upon roentgenograms. It compares the data obtained from this series with those from groups previously studied in a comparable manner, both in Europe and in the United States. It is not intended at this time to attempt to discover the causes of any differences found between the study and the reference series but merely to recognize and define any such differences. It is planned, however, to re-examine these children after six months and again after one year, and the present studies should serve as a base line from which to measure the progress of growth under known dietary and health conditions. Irregularities in the progress of growth and development can be attributed to health conditions with more confidence than can deviations from accepted norms for age. The purposes of collecting these data in this initial survey were to learn the characteristics of normal children in Marseilles and to develop the mechanism and techniques for future surveys there. One would have preferred to have this survey made prior to the war or at least prior to the marked restrictions in food supplies resulting therefrom. The latter, however, had been operative and increasing in severity for a period of six months to one year prior to the examination of the individual children.

As the majority of the children composing this series were obtained on the basis of family selection, the ages of those reporting for examinations could not be controlled. It became necessary, therefore, to divide these children into many age groups with small numbers in each. Year

The studies and observations on which this report is based were conducted with the support and under the auspices of the Rockefeller Foundation Health Commission and with the collaboration of the "Institut de Récherches d'Hygiene," established under the patronage of the Department of Health and Family of France. The authors are indebted to the staff of the section of nutrition of the Institute, especially to Doctors Bernard and Robert, for assistance in securing the data which are analyzed. The administration and the pediatric service of the Hospital of the Conception rendered valuable assistance in making space and facilities available for these studies.

and half-year age groups have been constructed through ten years, a deviation of three months from the birth date being allowed at all ages unless otherwise specified. Each of these age and sex groups contains from two to nine children, with the exceptions of the 6- and 10-year-olds. The latter groups were purposely enlarged by the addition of children recruited from the schools, and they contain between twenty-four and thirty-five of each sex at each age. The smaller groups do not justify the study of distributions, and the data presented give only the means of measurements, but the data from the 6- and 10-year-old age groups do allow for consideration of variability.

The selection of the standards most suitable for use in the interpretation of measurements derived from the children of Marseilles is difficult, because these children represent a very mixed racial stock, and none of the tables giving dependable normative data are based upon comparable groups. It has seemed preferable to compare these children with groups that have been carefully studied by technically comparable procedures, even though racial factors may explain any or all of the differences encountered, rather than to use less dependable data obtained from more similar children. Consistent differences thus demonstrated may be assumed to be real, and their interpretation is not complicated by problems of a technical nature.

Data obtained from studies of a small group of white children of North European stock (predominantly Irish), under 8½ years of age and re-examined periodically at the Harvard School of Public Health,*[1, 2] have been used as the standards for most measurements, because the techniques used in studying the children in Marseilles were modeled after the Boston studies in as many particulars as circumstances permitted.

The countries of birth of the parents and grandparents of each child were recorded as part of the clinical history. The majority of these were born in France, but a very considerable proportion (one or more in about 25 per cent of the families) were born in Italy and a few in Spain and other Mediterranean countries.

In order to have some measure of the effect of intermixture of Italian with French stock upon the size of the children studied, two sets of children were selected from the 6- and 10-year-olds on the basis of the country of birth of their parents. Only those children both of whose parents were known to have been born in France were included in the so-called French group, whereas only those whose parents were both born in Italy were grouped as Italian children. Although the means for most of the measurements were slightly smaller for the Italian than for the French group, the numbers in each were small, and the differences were not statistically significant.

Not only did the Boston children differ radically from the Marseilles group in racial and family background, but they had received regular

*The norms for body measurements based on the Boston studies and used in this report will be published shortly.

health service and dietary instruction, available to but few of the families enrolled in Marseilles. None of the children in the Boston group, for example, had ever shown either clinical or roentgenologic evidences of rickets, whereas a considerable proportion of the young infants in the Marseilles group presented evidence of at least minimum rickets, and a number showed other disturbances in bone growth, as described more fully below. It might be anticipated, therefore, that environmental factors would be found to have caused retardation in growth or other limitation in physical progress more commonly in the Marseilles than in the Boston series and that these retardations would be reflected in differences in the average measurements for the two groups.

As the norms for the Boston series do not extend through the entire age range under consideration, data on certain measurements obtained by Meredith[3] and by Boynton[4] on children in Iowa, which correspond closely with those obtained in Boston, have also been used in some of the charts for comparison at the older ages. In addition, data obtained by Gray and Ayres[5] from private school children in California have been used in some instances.

Several reports of measurements of French and Italian children have been found, but most of these have had to be discarded as a basis for comparison because of lack of information as to the ages included in the different groups, because of the failure to separate the data for the two sexes, or for other reasons. Comparisons have been made, however, for weight, height, and weight for height with school children of Paris studied by Fessard and co-workers[6] and with European children, principally French, living in Morocco and studied by Mathieu.*[7]

The data which are used in this study consist of five direct measurements, eleven measurements obtained from x-ray films of the leg, and ratings of osseous development as judged from films of the wrist and hand.

Body Size and Build.—Four measurements of body size were taken at all ages; that is, weight, recumbent length, chest circumference, and pelvic breadth.† Standing height was also taken at 3 years of age and thereafter.

In Tables I and II the means for these measurements are presented for boys and girls, respectively, and the number of subjects entering the calculations at each age are given. In Charts 1 through 4 these means are plotted against the Boston norms. Although many of the differences between the study and the reference data are not statistically significant

*The range of ages included in the various norms for different age groups was somewhat different from the ranges allowed in the Marseilles series. In the Boston series it was possible to restrict the variation very sharply (i.e. plus and minus one week at six months and increasing to plus and minus three weeks at six and one-half years), whereas in the Iowa, California, Paris and Morocco series the ages given are for the nearest birthday and, therefore, include a range of one year. The Marseilles age groups have been restricted to variation of plus and minus three months, except in Tables IV, V and VIII, for which the groupings have been changed to include all children within six months of the age given.

†The bi-iliocristal measurement was used for pelvic breadth; that is, the breadth between the crests of the ilia, taken with sliding wooden calipers.

TABLE I

MEANS OF BODY MEASUREMENTS FOR BOYS

AGE	WEIGHT		LENGTH		HEIGHT		CHEST CIRCUMFERENCE		PELVIC BREADTH	
	NUMBER OF CASES	MEAN (KG.)	NUMBER OF CASES	MEAN (CM.)	NUMBER OF CASES	MEAN (CM.)	NUMBER OF CASES	MEAN (CM.)	NUMBER OF CASES	MEAN (CM.)
6 mo.	5	6.91	5	63.4			5	41.7	5	11.9
9 mo.	3	6.88	3	65.9			3	42.1	3	11.5
1 yr.	5	7.80	5	72.0			5	44.4	4	12.5
1½ yr.	7	10.51	7	79.2			7	47.8	6	14.2
2 yr.										
2½ yr.	3	13.17	3	87.5			3	51.0	3	14.8
3 yr.	7	13.42	7	91.6	7	90.8	7	51.8	7	15.8
3½ yr.	4	14.24	4	94.7	3	92.9	4	51.6	3	16.6
4 yr.	6	14.69	6	99.0	6	96.5	6	53.2	5	17.0
4½ yr.	4	15.93	4	99.9	2	99.7	4	54.5	4	17.2
5 yr.	4	15.64	5	101.1	5	100.1	5	53.6	5	16.9
5½ yr.	5	17.17	5	104.1	5	103.1	5	55.2	5	17.6
6 yr.	36	18.83	38	108.7	37	107.8	38	56.1	38	18.5
6½ yr.	4	20.57	4	114.4	4	113.4	4	57.2	4	19.6
7 yr.	4	21.08	4	115.1	4	114.1	4	57.6	4	20.0
7½ yr.	4	21.90	4	118.5	4	118.1	4	59.1	4	20.2
8 yr.	6	20.74	6	116.4	6	115.7	6	57.6	6	19.2
8½ yr.										
9 yr.										
9½ yr.	3	25.78	3	129.6	3	129.4	3	63.5	3	20.7
10 yr.	25	27.05	21	131.3	24	130.5	23	62.8	21	22.0

TABLE II

MEANS OF BODY MEASUREMENTS FOR GIRLS

AGE	WEIGHT		LENGTH		HEIGHT		CHEST CIRCUMFERENCE		PELVIC BREADTH	
	NUMBER OF CASES	MEAN (KG.)	NUMBER OF CASES	MEAN (CM.)	NUMBER OF CASES	MEAN (CM.)	NUMBER OF CASES	MEAN (CM.)	NUMBER OF CASES	MEAN (CM.)
6 mo.	9	6.37	9	62.1			9	41.3	8	11.4
9 mo.	4	7.8	4	68.4			4	42.7	4	12.0
1 yr.	10	8.13	10	69.4			10	44.5	10	12.5
1½ yr.	4	9.88	4	76.1			4	47.6	4	14.0
2 yr.	3	10.66	3	77.9			3	48.2	3	14.2
2½ yr.	2	11.40	2	83.1	2	81.9	2	50.2	2	15.0
3 yr.	9	12.4	9	88.3	6	87.4	9	50.6	9	15.5
3½ yr.	4	15.0	4	92.1	4	91.6	4	54.0	4	16.6
4 yr.										
4½ yr.	2	14.6	2	96.9	2	96.7	2	54.2	2	17.2
5 yr.	11	17.08	11	103.6	11	101.5	11	54.6	10	17.5
5½ yr.	4	17.07	4	106.57	4	105.5	4	53.2	4	17.8
6 yr.	26	18.05	25	108.6	25	107.81	26	54.1	26	18.6
6½ yr.	4	17.15	4	109.0	4	107.3	4	54.9	4	17.8
7 yr.	2	22.67	2	116.5	2	115.5	2	60.2	2	18.5
7½ yr.	2	20.97	2	117.9	2	120.4	2	58.7	2	19.6
8 yr.	4	21.71	3	121.5	4	121.5	4	56.8	4	19.9
8½ yr.	6	23.19	3	122.0	6	121.4	5	57.8	4	20.5
9 yr.	6	22.64	4	119.8	6	123.2	6	56.5	5	19.7
9½ yr.	3	26.50	2	133.2	3	129.3	3	60.1	3	21.9
10 yr.	25	25.63	21	127.4	25	127.1	22	58.7	22	21.2

at any one age, the consistency of some of these differences at successive ages and for both sexes make them deserving of attention.

Chart 1 shows that the children in the Marseilles series never have as high an average weight for age as do the Boston children. Most of the means for the former are from one to two sigma below those for the latter. The boys of 6, 9, and 12 months hold a lower position than those at later ages, but as this is not so apparent in the case of girls and as the numbers are small, this observation may be due entirely to the chance of sampling.

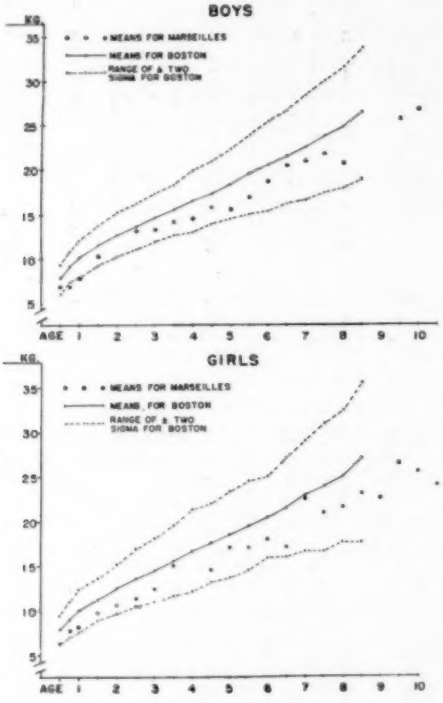

Chart 1.—Body weight.

Chart 2 shows a very similar situation in respect to body length, except that most points formed by the Marseilles means are nearer to the minus two sigma curve and more are below. When one recalls that 95 to 100 per cent of the Boston children would take a position above this lower curve, the striking difference in the body length of the two groups is appreciated.

Chart 3 shows that the Marseilles and the Boston series are more alike in respect to chest circumference than in body weight or length, though there is still a tendency for the means for chest circumference to be lower in the former instance, especially between 6 and 18 months of age.

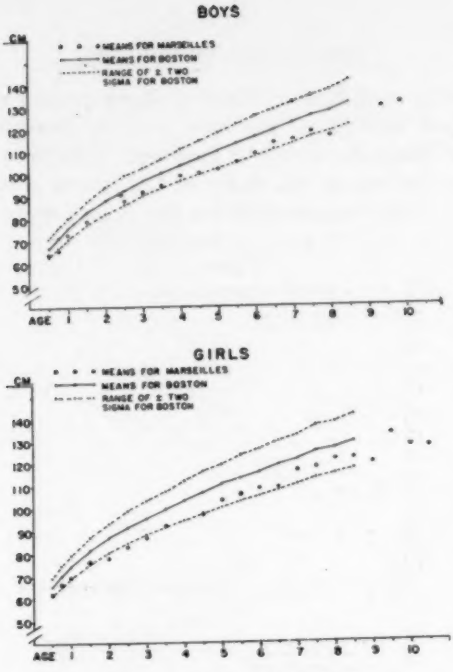

Chart 2.—Recumbent length.

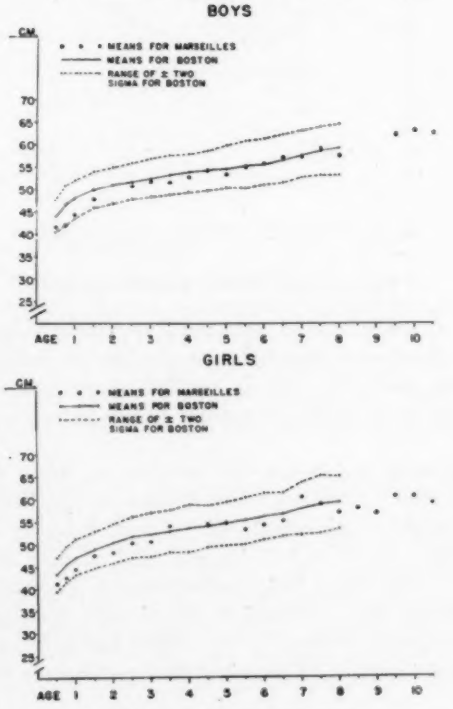

Chart 3.—Chest circumference.

Pelvic breadth, as plotted in Chart 4, shows greater variability than might have been anticipated for such a stable measurement, but the position of the Marseilles means at most ages is between the curves for the means and the minus two sigma of the Boston series. Norms are not available for this measurement for the Boston group below 2 years of age.

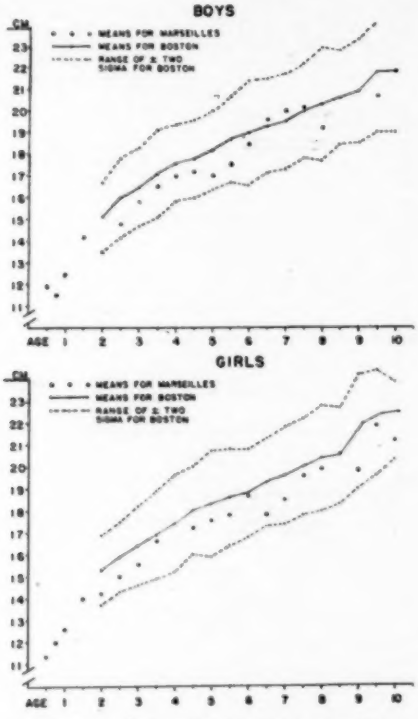

Chart 4.—Bi-iliocristal breadth of pelvis.

From these charts it appears that the Marseilles children of both sexes are strikingly short as contrasted with the Boston children, moderately light in weight, and only slightly smaller in chest and pelvis. These differences tend to be relatively greater before than after 18 months of age.

Chart 5 presents the means for weights in Marseilles against the means for weights of various other groups in the United States and abroad. In reading this chart, one should keep in mind that the Marseilles, Boston, Iowa, and California children were all weighed without clothing or with but a light undergarment, whereas the Paris and Moroccan children were weighed in school with clothing. It is of interest that the points formed by the means for weights of the French groups fall close together. The points representing the Marseilles means

for ages 5½ through 10½ fall somewhat below those for Paris and Morocco, but this may be explained by the factor of clothing or even by mere chance.

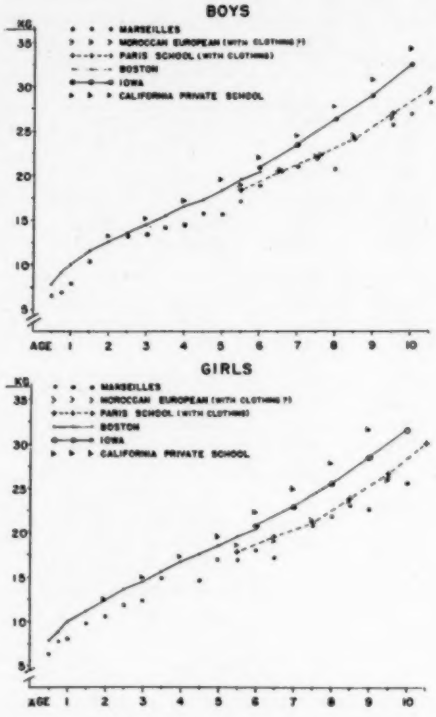

Chart 5.—Body weights from various sources.

Chart 6 makes it possible to compare these same groups without the complicating factor of differences in clothing, using standing height as the measurement. Here all the French means are very close together at most ages for which there are data from the different sources. The consistently and markedly higher position of the figures from all the American series is striking, as is also the outstanding stature of the private school children in California.

In order to make the age groupings more alike for purposes of comparison, the children of school age in Marseilles have been regrouped into full-year categories and the means for certain measurements calculated for these larger units. Full-year groups have been formed with the birthday the midpoint of the year for comparison with the Iowa and California norms, and the means for weight, height, and pelvic breadth are presented in Table III. Other full-year groups have been formed with the half year of age as the midpoint. These have been

TABLE III*

MEANS FOR BODY MEASUREMENTS OF SCHOOL CHILDREN
COMPARISON BETWEEN MARSEILLES DATA AND AMERICAN NORMS

	BOYS			GIRLS		
	MARSEILLES	IOWA	CALIFORNIA	MARSEILLES	IOWA	CALIFORNIA
5½-6½ yr.						
Weight	19.0	20.9	22.22	17.94	20.6	22.40
Stature	108.16	115.7	118.59	108.0	115.0	118.05
Pelvic breadth	18.58	19.1	19.25	18.71	18.6	18.97
6½-7½ yr.						
Weight	21.92	23.5	24.64	20.33	22.9	25.14
Stature	116.52	121.9	124.72	112.74	120.9	124.10
Pelvic breadth	20.12	19.8	19.99	18.72	19.7	19.63
7½-8½ yr.						
Weight	20.66	26.3	27.92	21.60	25.7	27.90
Stature	115.22	128.1	131.06	101.63	126.7	130.74
Pelvic breadth	19.31	20.60	20.98	19.62	20.5	20.84
8½-9½ yr.						
Weight	24.45	29.0	30.89	22.80	28.50	31.76
Stature	124.3	133.7	135.83	123.78	132.5	135.91
Pelvic breadth		21.4	21.53	20.02	21.1	21.51
9½-10½ yr.						
Weight	26.15	32.5	34.45	27.77	21.1	21.51
Stature	130.26	138.90	141.19	131.65	137.7	140.12
Pelvic breadth	20.90	22.2	22.23		21.9	22.29

*Weights are given in kilograms and linear measurements in centimeters in Tables III, IV, and V.

TABLE IV

MEANS FOR BODY MEASUREMENTS OF SCHOOL CHILDREN
COMPARISON BETWEEN MARSEILLES DATA AND EUROPEAN NORMS

	BOYS			GIRLS		
	MARSEILLES	PARIS	MOROCCO	MARSEILLES	PARIS	MOROCCO
5-6 yr.						
Weight	17.71	18.44	19.00	17.94	17.81	18.67
Stature	104.4	107.9	111.00	106.85	106.90	110.2
6-7 yr.						
Weight	21.23	20.40	20.33	18.67	19.52	19.19
Stature	114.91	113.6	113.5	109.18	112.6	112.4
7-8 yr.						
Weight	20.94	22.23	22.28	20.94	21.20	21.35
Stature	115.30	117.7	118.2	118.90	116.40	117.70
8-9 yr.						
Weight	21.46	24.26	24.56	22.69	23.99	23.63
Stature	117.23	121.8	123.8	121.97	122.3	122.9
9-10 yr.						
Weight	25.47	27.03	26.97	24.45	26.76	26.10
Stature	127.88	127.9	128.8	128.42	127.7	127.9

used for comparison with the Paris and Moroccan norms, and the means for weight and stature are presented in Table IV. It should be pointed out again that the weights for Paris and Moroccan children are with clothing. These tables are based upon somewhat larger groups of children than are the points in the preceding charts, but the impressions gained from the two sets of data are quite similar.

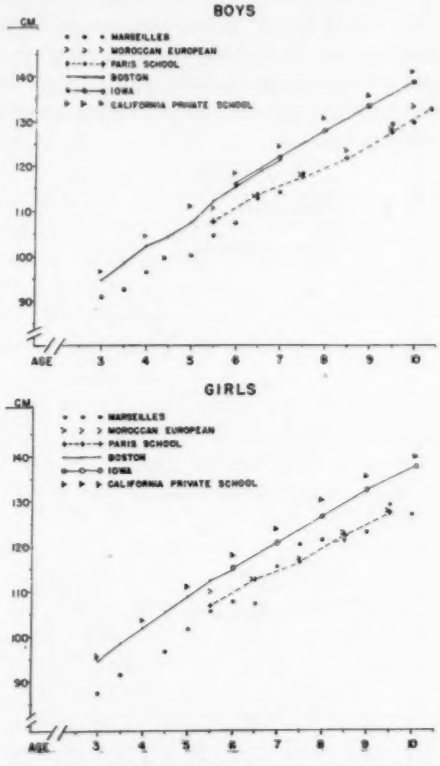

Chart 6.—Standing heights from various sources.

It is of interest that if one were to grade the children in these different groups on the basis of their relative social and economic circumstances, as judged from the descriptions given in connection with the published data, the California children would come at the top, the Iowa group easily second, and the Boston series third. The order of the French groups cannot be given, but the Paris and the Marseilles series are probably quite alike in social and economic status.

An attempt has been made in Chart 7 to overcome the difficulties introduced by differences in the average heights of the several series of children which have been compared. The average height of Marseilles children at each age has been used to find the average weight for this height

and age on various height-weight tables. Against these have been plotted the average weights for all Marseilles children. The tables used for reference were based on the same studies as those already utilized, except that figures for the United States as a whole, as originally published by Woodbury[8] and by Baldwin and Wood[9] have been substituted for figures from Iowa. These curves show that the Marseilles children are usually close to the children in the other series in weight for height.* On the basis of weight for height alone, there appears to be no evidence of undernutrition among the Marseilles children, but the fundamental differences in build already demonstrated and further revealed by the measurements from roentgenograms make caution necessary in the interpretation of this finding.

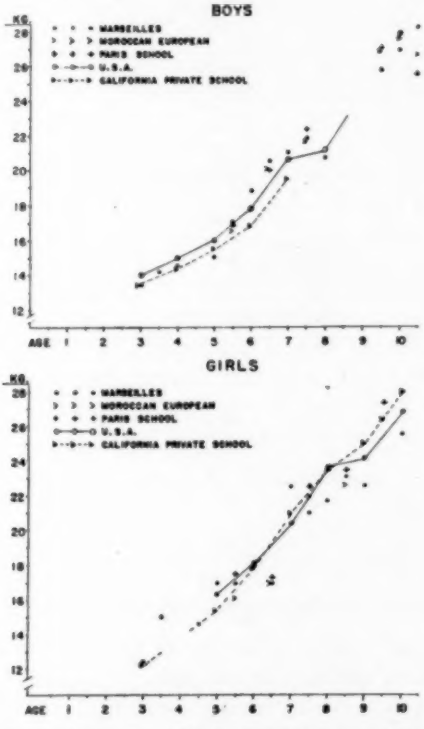

Chart 7.—Comparisons of weights for heights from selected groups.

One further test of the data for the 6- and 10-year-old children has been made with the purpose of interpreting weight in terms of build. The tables of Prior[10] have been used for they take into account pelvic breadth as well as height, age, and sex in arriving at an expected weight. According to these standards, 50 of 105 children are more than 1.5 kg.

*The use of the average weight of all children in the Marseilles series, rather than the weight of those of average height only, introduces a difference which may reduce the value of this comparison.

underweight, in contrast to but five who are more than 1.5 kg. overweight. The 6-year-old girls and the 10-year-old boys and girls are alike in being very uniformly below weight. Not one child in these groups exceeded the standard by more than 0.5 kg. The 6-year-old boys, however, show an interesting difference from the girls not observed in the 10-year-old boys. At 6 years of age twenty-six boys are above expected weight (eight more than 1.5 kg.), and only ten are below (only three more than 1.5 kg.). The numbers seem adequate to make this finding of probable significance, but it is not in keeping with other data considered elsewhere. It will be seen later, however, that Marseilles boys tend to exceed Boston boys in amount of calf muscle, whereas the reverse is true in the case of girls. On the basis of the Prior norms, one would seem justified in concluding that the Marseilles children are, with the exception of 6-year-old boys, appreciably underweight for body build.

Table V presents the means and sigmas for the measurements already considered for the 6- and 10-year-old children. They are compared with figures derived from the Boston series at 6 years and with those from Iowa at 10 years. The sigmas do not suggest any unusual features of the distributions at these ages.

In order to rule out age as a factor and to consider each child from the standpoint of his position in respect to the normal distribution (according to the Boston norms), each measurement for each child from 1 through 8 years of age has been given a ranking on a five-point scale: one plus (+) has been used to denote a position lower than minus two sigma; two plus (++) to denote lower than minus one but not lower than minus two sigma; three plus (+++) between and including plus and minus one sigma; four plus (++++), corresponding to two plus (++), and five plus (+++++), corresponding to one plus (+), but above the mean. Tables VI and VII show the number of children in each of these ranks at each age for each of the four body measurements. The additions at the bottom of the columns in these tables show the preponderance of children in Marseilles with ratings below three plus. In contrast to the 18 per cent which would be expected to have less than three plus (either + or ++) ratings, the following percentages are revealed by these figures:

	BOYS	GIRLS
Weight	46.5%	45.5%
Length	75.7%	68.6%
Chest circumference	21.4%	30.7%
Pelvic breadth	21.2%	18.4%

No boy has a five plus rank, and only two each have a four plus rank for either weight or length. No girl attains greater than three plus for either of these measurements against an expected 18 per cent for each. Four plus ranks are more commonly attained for chest circumference and pelvic breadth, but even in these the percentages are not up to those to be expected if the Marseilles children are similar to those in Boston.

TABLE V

MEANS AND SIGMAS OF BODY MEASUREMENTS OF SIX- AND TEN-YEAR-OLD CHILDREN COMPARISON BETWEEN MARSEILLES DATA AND AMERICAN NORMS

	BOYS		GIRLS	
Six Years Old	MEANS	SIGMAS	MEANS	SIGMAS
Weight				
Marseilles	18.83	2.38	18.05	2.06
Boston	20.6	2.5	20.3	2.3
Length				
Marseilles	108.73	5.01	108.6	4.06
Boston	116.7	4.5	115.8	5.1
Height				
Marseilles	107.85	4.67	107.81	4.35
Boston	115.5	4.5	114.7	5.1
Chest circumference				
Marseilles	56.11	2.26	54.18	2.66
Boston	56.4	2.5	56.0	2.6
Pelvic breadth				
Marseilles	18.49	1.12	18.63	1.10
Boston (Bi-iliocristal)	19.0	1.2	18.8	1.0
Ten Years Old				
Weight				
Marseilles	27.05	3.19	26.63	3.29
Iowa City	32.5	5.53	31.6	5.34
Length				
Marseilles	131.37	5.50	127.40	6.35
Iowa City				
Height				
Marseilles	130.55	4.70	127.13	6.90
Iowa City	138.9	5.6	137.7	5.7
Chest circumference				
Marseilles	63.50	4.11	60.21	2.95
Iowa City				
Pelvic breadth				
Marseilles	22.0	1.35	21.20	1.20
Iowa City (Bi-iliocristal)	22.2	1.28	21.90	1.46

Table VIII presents the ranks held by the older children in Marseilles, using the norms from Iowa for purposes of ranking and including in the yearly age groups all children to their nearest birthday. This table shows that the older children have substantially the same abnormalities in the several distributions, with respect to these norms, as do those in the younger age groups with respect to the Boston norms. The percentages with ratings of less than three plus are as follows:

	BOYS	GIRLS
Weight	42.8%	43.2%
Standing height	68.2%	57.4%
Pelvic breadth	20.0%	23.5%

Table VI

Ranks for Body Measurements for Boys

Marseilles Children Related to Boston Norms

Age (yr.)	Weight					Length					Chest Circumference					Pelvic Breadth				
	+	++	+++	++++	+++++	+	++	+++	++++	+++++	+	++	+++	++++	+++++	+	++	+++	++++	+++++
1	4	1				3		2			2	3				1	3			
1½	2	3	2			2	1	4			1	1	5					5	1	
2	1					1					1						1			
2½		1	2			1	1		1			1	2			1			2	
3	2	2	3			3	1	2	1			1	6			1	1	3	2	
3½		2	2			2	1	1				2	2				1	1	1	
4		3	3			3	3					1	5				1	3	1	
4½		2	2			1	3						4					4		
5	1	1	2			2	2	1				1	4				2	3		
5½		3	1	1		3	1	1					4		1		1	4		
6	1	10	24	1		16	14	8			2	3	21	10	2	2	5	28	3	
6½		1	3				3	1					4					4		
7		1	3			2	1	1					4					3	1	
7½		2	2			2	1	1					4					3	1	
8	1	2	3			5	1					2	4				2	4		
Totals	12	34	52	2		46	33	22	2		6	15	69	10	3	5	17	65	12	
Grand total	100					103					103					99				
Per cent	12	34	52	2		45	32	21	2		6	14	67	10	3	5	17	66	12	

TABLE VII

RANKS FOR BODY MEASUREMENTS FOR GIRLS

MARSEILLES CHILDREN RELATED TO BOSTON NORMS

AGE (YR.)	WEIGHT					LENGTH					CHEST CIRCUMFERENCE					PELVIC BREADTH				
	+	++	+++	++++	+++++	+	++	+++	++++	+++++	+	++	+++	++++	+++++	+	++	+++	++++	+++++
1	4	2	4			3	5	2			3	3	4				3	4	2	1
1½		2	2			1	2	1				1	3					2	2	
2	1	1	1			2	1				1	1		1				3		
2½		1	1			1	1					1	1					1	1	
3		6	3			5	2	2				4	4	1			2	5	2	
3½	1		3			1	1	2					3	1				3	1	
4																				
4½		2				1	1						2					2		
5	1	2	8			4	3	4				2	9			1	1	6	1	1
5½		2	2			1	3					2	2				1	3		
6	5	6	15			7	8	10			2	6	17	1		1	4	16	4	1
6½	1	2	1			2	1	1				1	3			1		3		
7			2				1	1					1	1			1	1		
7½			2			1		1					2					2		
8		1	3				1	2					4					4		
Totals	13	27	47			29	30	26			6	21	55	5		3	12	55	13	3
Grand total	87					85					87					86				
Per cent	15	31	54			34	35	31			7	24	63	6		3.5	14	64	15	3.5

TABLE VIII

RANKS FOR BODY MEASUREMENTS SIX THROUGH TEN YEARS
MARSEILLES CHILDREN RELATED TO IOWA NORMS

AGE (YR.)	WEIGHT					STANDING HEIGHT					PELVIC BREADTH				
	+	++	+++	++++	+++++	+	++	+++	++++	+++++	+	++	+++	++++	+++++
Boys															
6	4	10	20	1	1	15	13	9			6	3	27	2	
7		3	4			2	1	3		1			4	2	1
8	1	4	4			5	1	3				2	7		
10	1	13	18			5	15	10				5	12	2	1
Totals	6	30	46	1	1	27	30	25		1	6	10	50	6	2
Grand total	84					83					74				
Per cent	7	36	55	1	1	33	36	30		1	8	13.5	67.5	8	3
Girls															
6	1	10	17			12	5	10			1	4	19	3	
7		2	3			1	2	2				1	3	1	
8		2	5				3	4				1	4		
9	1	3	7			1	3	7			1	1	3		
10	3	13	14			10	10	10			1	5	15	1	
Totals	5	30	46			24	23	35			3	12	44	5	
Grand total	81					82					64				
Per cent	6	37	57			29	28	43			5	19	69	7	

Measurements From Roentgenograms.—Charts 8 to 15, inclusive, present data obtained from x-ray films of the right leg, taken and measured according to a standard technique previously described.* [2] The means for the x-ray measurements obtained in Marseilles are plotted against the means and ranges for the same measurements taken on the Boston group. These data, in the main, confirm the observations made on the basis of the direct body measurements. The shaft of the tibia (Chart 8) appears to be just as short in comparison with the standard as is body length (Chart 2). The points representing breadth measurements (Charts 9, 10, and 11) usually fall near to the curve representing the standard mean, although more points on most of the charts fall below rather than above that line, especially on those representing skin and subcutaneous tissue. The means for these linear measurements are given in Tables IX and X.

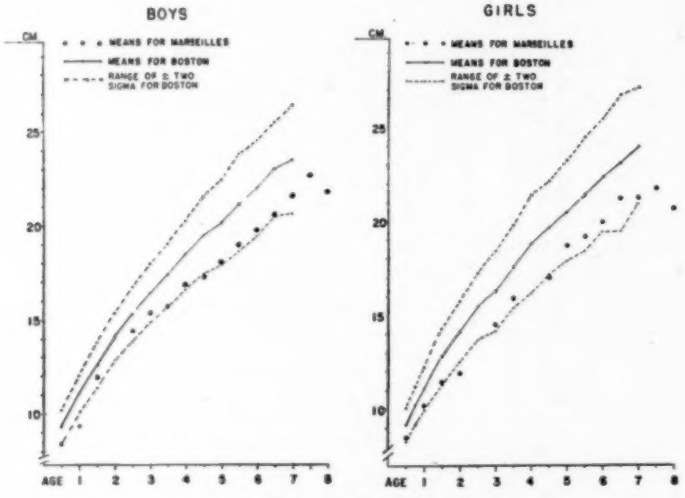

Chart 8.—Length of shaft of tibia by x-ray.

Charts 12 to 15, inclusive, are based upon the weights of the film segments representing the shadows of the entire tibial shaft region of the leg, and the portion of this region appearing to be bone, muscle, and subcutaneous tissue, respectively. In these charts the weight of film area has been divided by the length of tibial shaft to give an index of the amount of tissue per unit of length. In this way the differences in length between the Marseilles and Boston children are taken out and the amount of each tissue for age and length may be considered. There

*According to this technique, the right leg is held fully extended and in contact with the cassette. An anteroposterior view is taken at three-foot tube distance from the cassette, and exposure is so judged as to assure clear outlines to the bones and soft tissues. The area of film included between parallel lines drawn tangent to the ends of the shaft of the tibia is studied from the standpoint of length and breadth measurements and of areas of film shadows representing the different tissues. These shadow areas are cut out and weighed and expressed as grams of film.

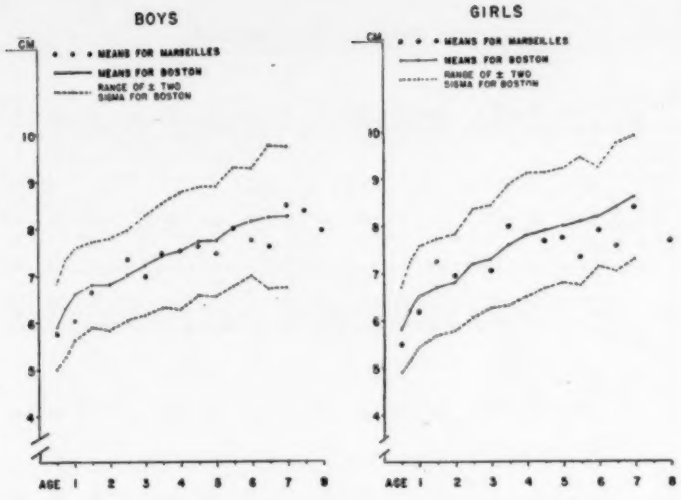

Chart 9.—Total breadth of calf by x-ray.

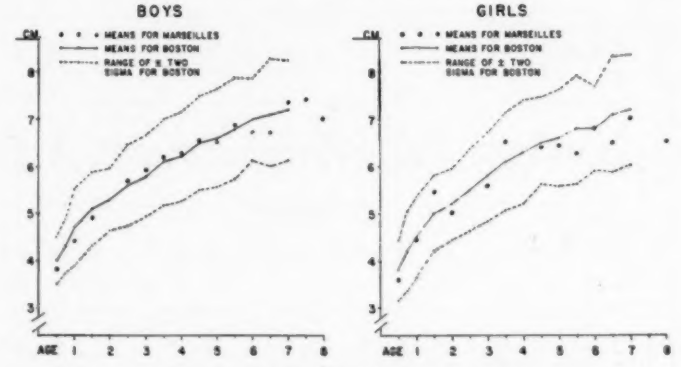

Chart 10.—Breadth of calf muscle by x-ray.

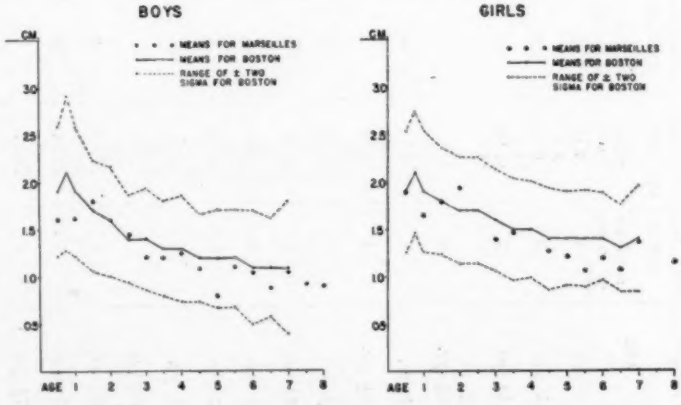

Chart 11.—Breadth of two thicknesses of skin and subcutaneous tissue in calf by x-ray.

TABLE IX

MEANS FOR LINEAR MEASUREMENTS FROM ROENTGENOGRAMS OF BOYS

AGE	LENGTH OF TIBIA		BREADTH OF CALF		BREADTH OF HEAD OF TIBIA		BREADTH OF SHAFT OF TIBIA		BREADTH OF MUSCLE		BREADTH OF SKIN & SUBCUT. TISSUE	
	NUMBER OF CASES	MEAN (CM.)	NUMBER OF CASES	MEAN (CM.)	NUMBER OF CASES	MEAN (CM.)	NUMBER OF CASES	MEAN (CM.)	NUMBER OF CASES	MEAN (CM.)	NUMBER OF CASES	MEAN (CM.)
6 mo.	3	8.41	3	5.76	2	2.5	2	0.925	2	3.8	2	1.60
		9.3		*5.9*		*2.6*		*1.0*		*4.0*		*1.9*
1 yr.	3	9.36	4	6.02	4	2.77	4	1.12	4	4.41	4	1.61
		11.1		*6.6*		*3.0*		*1.1*		*4.7*		*1.9*
1½ yr.	5	11.96	4	6.67	5	3.30	5	1.23	5	4.90	5	1.80
		12.6		*6.8*		*3.4*		*1.3*		*5.1*		*1.7*
2 yr.												
2½ yr.	3	14.4	3	7.33	3	3.80	3	1.33	3	5.7	3	1.45
		15.3		*7.0*		*4.0*		*1.5*		*5.6*		*1.4*
3 yr.	6	15.31	6	6.98	6	3.96	6	1.49	6	5.92	6	1.21
		16.4		*7.2*		*4.2*		*1.6*		*5.8*		*1.4*
3½ yr.	3	15.74	3	7.45	3	3.96	3	1.56	3	6.20	3	1.21
		17.4		*7.4*		*4.4*		*1.6*		*6.1*		*1.3*
4 yr.	5	16.89	5	7.49	5	4.36	5	1.40	4	6.28	5	1.26
		18.5		*7.5*		*4.5*		*1.7*		*6.2*		*1.3*
4½ yr.	3	17.28	3	7.60	3	4.46	3	1.58	3	6.56	3	1.08
		19.5		*7.7*		*4.6*		*1.7*		*6.5*		*1.2*
5 yr.	5	18.08	5	7.46	5	4.61	5	1.59	5	6.49	5	0.88
		20.2		*7.7*		*4.7*		*1.7*		*6.6*		*1.2*
5½ yr.	5	18.34	5	7.99	5	4.52	5	1.67	5	6.88	5	1.11
		21.2		*8.0*		*4.8*		*1.8*		*6.8*		*1.2*
6 yr.	35	19.8	35	7.72	35	4.85	35	1.77	35	6.72	35	1.05
		22.0		*8.1*		*4.9*		*1.8*		*7.0*		*1.1*
Sigma		1.4		0.6		0.2		0.3		0.46		0.30
		1.3		*0.56*		*0.25*		*0.14*		*0.44*		*0.3*
6½ yr.	4	20.51	4	7.57	4	4.97	4	1.86	4	6.72	3	0.86
		23.0		*8.2*		*5.1*		*1.8*		*7.1*		*1.1*
7 yr.	4	21.52	4	8.45	4	5.02	4	1.82	4	7.38	4	1.06
		23.5		*8.2*		*5.2*		*1.9*		*7.2*		*1.1*
7½ yr.	4	22.77	4	8.35	4	5.05	4	1.81	4	7.42	4	0.925
		—		—		—		—		—		—
8 yr.	5	21.8	5	7.91	5	5.02	5	1.84	5	7.01	5	0.90
		—		—		—		—		—		—

Figures in italics give the corresponding means for the Boston series.

TABLE X

MEANS FOR LINEAR MEASUREMENTS FROM ROENTGENOGRAMS OF GIRLS

AGE	LENGTH OF TIBIA		BREADTH OF CALF		BREADTH OF HEAD OF TIBIA		BREADTH OF SHAFT OF TIBIA		BREADTH OF MUSCLE		BREADTH OF SKIN & SUBCUTANEOUS TISSUE	
	NUMBER OF CASES	MEAN (CM.)	NUMBER OF CASES	MEAN (CM.)	NUMBER OF CASES	MEAN (CM.)	NUMBER OF CASES	MEAN (CM.)	NUMBER OF CASES	MEAN (CM.)	NUMBER OF CASES	MEAN (CM.)
6 mo.	5	8.50	5	5.50	5	2.48	5	.96	5	3.60	5	1.90
		9.2		*5.8*		*2.5*		*1.0*		*3.8*		*1.9*
1 yr.	9	10.21	9	6.20	9	2.62	9	1.00	9	4.45	9	1.64
		11.1		*6.5*		*2.9*		*1.1*		*4.5*		*1.9*
1½ yr.	4	11.47	3	7.24	3	3.10	2	1.30	3	5.46	3	1.78
		12.8		*6.7*		*3.4*		*1.3*		*5.0*		*1.8*
2 yr.	3	11.93	3	6.96	3	3.46	3	1.30	3	5.02	3	1.93
		14.2		*6.8*		*3.7*		*1.4*		*5.2*		*1.7*
3 yr.	7	14.65	7	7.08	7	3.65	7	1.38	7	5.59	7	1.49
		16.3		*7.3*		*4.1*		*1.5*		*5.8*		*1.6*
3½ yr.	4	15.95	4	8.0	4	4.17	4	1.60	4	6.53	4	1.47
		17.6		*7.6*		*4.2*		*1.6*		*6.1*		*1.5*
4½ yr.	2	17.15	2	7.7	2	4.15	2	1.55	2	6.42	2	1.27
		19.7		*7.9*		*4.4*		*1.7*		*6.5*		*1.4*
5 yr.	9	18.68	9	7.77	9	4.45	9	1.65	9	6.44	9	1.22
		20.6		*8.0*		*4.5*		*1.7*		*6.6*		*1.4*
5½ yr.	4	19.5	3	7.35	3	4.40	3	1.58	4	6.5	4	1.10
		21.5		*8.1*		*4.6*		*1.8*		*6.8*		*1.4*
6 yr.	25	19.9	25	7.97	25	4.32	25	1.75	25	6.85	25	1.24
		22.4		*8.2*		*4.7*		*1.8*		*6.8*		*1.4*
Sigma		1.30		0.6		0.2		0.2		0.5		0.3
		1.45		*0.52*		*0.25*		*0.12*		*0.45*		*0.22*
6½ yr.	4	21.30	4	7.58	4	4.57	4	1.68	4	6.51	4	1.07
		23.2		*8.4*		*4.8*		*1.8*		*7.1*		*1.3*
7 yr.	2	21.35	2	8.4	2	4.70	2	1.92	2	7.02	2	1.37
		24.1		*8.6*		*4.9*		*1.8*		*7.2*		*1.4*
8 yr.	3	20.76	3	7.70	3	4.80	3	1.91	3	6.55	3	1.14
		—		—		—		—		—		—
8½ yr.	4	23.01	4	8.30	4	4.92	4	1.92	4	7.15	4	1.15
		—		—		—		—		—		—
9 yr.	6	24.46	6	8.16	6	5.01	6	1.89	6	7.24	6	0.92
		—		—		—		—		—		—

Figures in italics give the corresponding means for the Boston series.

were not enough satisfactory films obtained on Marseilles children at certain ages to justify plotting the means so that these graphs are not complete, but the points available suggest the following differences between the two groups of children. The bones of the Marseilles children,

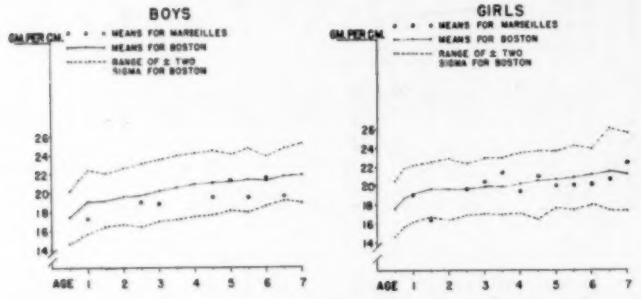

Chart 12.—Weight of area of total calf on x-ray film per unit of tibial length.

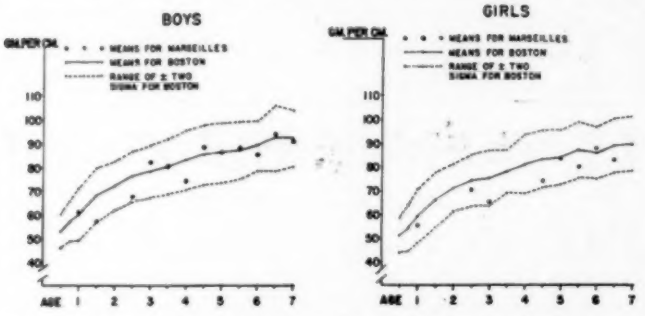

Chart 13.—Weight of area of bone on x-ray film per unit of tibial length.

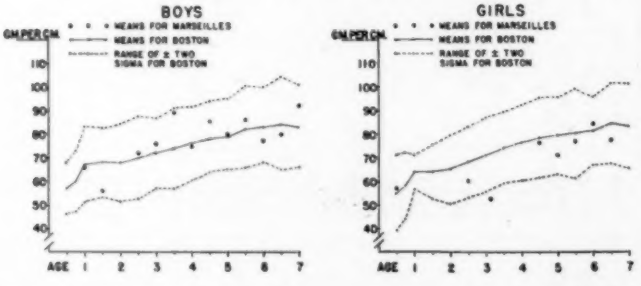

Chart 14.—Weight of area of muscle on x-ray film per unit of tibial length.

especially of the girls, are rather small or slender for length. The muscles tend to be above average for boys and below for girls, constituting a rather striking sex difference. The amount of skin and subcutaneous tissue shows no consistent difference between the Marseilles

and Boston children of either sex when differences in length of leg are excluded. The means for these weights of film shadows are given in Tables XI and XII.

The conclusions to be drawn from these data on body build are that the children studied in Marseilles are strikingly short in comparison with children in Paris. They are not, however, after 1 year of age particularly narrow of pelvis or small in chest circumference and are not underweight for height and age although somewhat so when pelvic breadth is also taken into account. These children, therefore, are not uniformly smaller than the standard groups but are rather of short and stocky build. The data for body weight certainly do not support the view that any large proportion of these children are underweight to any marked degree. This does not, of course, mean that they are up to ideal weight for their build or that they have gained in a satisfactory manner during the months immediately preceding their examinations.

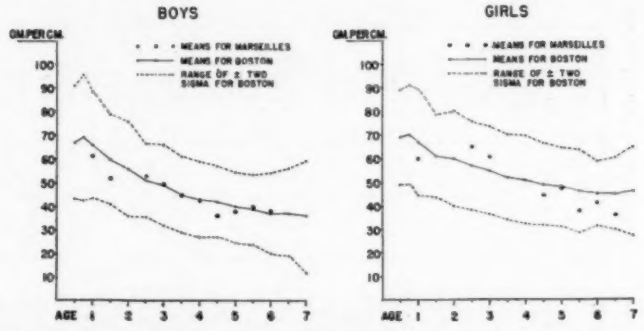

Chart 15.—Weight of area of skin and subcutaneous tissue on x-ray film per unit of tibial length.

These data suggest a preponderance of racial over environmental factors after early infancy in determining general body size and build. The Marseilles averages for infants under 2 years of age, however, tend to fall below the levels which might be expected on the basis of the positions held by older children. This suggests that there may have been some retardation of growth among the young infants, but owing to the small number of subjects in each group, this age difference may result from the chance of sampling.

Developmental Status.—It is of interest to compare the Marseilles children with American children in other developmental attributes besides size and build. A number of observations were made for this purpose as part of the clinical examinations; for example, size of fontanel, number of erupted teeth, shape of head and chest, posture, and gait. The number of children examined at each age, however, was not sufficient to make differences in these ratings significant, especially since some of them were very subjective evaluations. Delay in closure of the fontanel

TABLE XI

MEANS FOR MEASUREMENTS OF AREAS FROM ROENTGENOGRAMS OF BOYS

AGE (YR.)	TOTAL LEG AREA		BONE AREA		MUSCLE AREA		BONE AND MUSCLE AREA		SKIN AND SUBCUTANEOUS TISSUE AREA	
	NUMBER OF CASES	MEAN (C.C.)	NUMBER OF CASES	MEAN (C.C.)	NUMBER OF CASES	MEAN (C.C.)	NUMBER OF CASES	MEAN (C.C.)	NUMBER OF CASES	MEAN (C.C.)
1	2	1.773	2	0.572	2	0.624	2	1.196	2	0.577
		2.15		*0.67*		*0.75*		*1.42*		*1.9*
1½	3	1.961	3	0.683	3	0.672	3	1.356	3	0.606
		2.46		*0.86*		*0.86*		*1.72*		*1.7*
2										
2½	3	2.729	3	.956	3	1.013	3	1.99	3	0.760
		3.00		*1.17*		*1.07*		*2.23*		*1.4*
3	4	3.121	4	1.254	4	1.163	4	2.417	4	0.702
		3.26		*1.28*		*1.19*		*2.46*		*1.4*
3½	2	3.378	2	1.257	2	1.405	2	2.662	2	0.710
		3.47		*1.39*		*1.29*		*2.69*		*1.3*
4	4	3.280	4	1.249	4	1.262	4	2.511	4	0.714
		3.74		*1.53*		*1.41*		*2.94*		*1.3*
4½	2	3.637	2	1.525	2	1.496	2	3.021	2	0.616
		4.00		*1.66*		*1.53*		*3.18*		*1.2*
5	4	3.632	4	1.553	4	1.467	4	2.946	4	0.686
		4.17		*1.74*		*1.61*		*3.34*		*1.2*
5½	4	3.695	4	1.612	4	1.605	4	3.212	4	0.733
		4.42		*1.85*		*1.76*		*3.60*		*1.1*
6	30	4.166	30	1.767	30	1.567	30	3.300	30	0.759
		4.63		*1.96*		*1.85*		*3.81*		*1.1*
Sigma		0.582		0.224		0.251		0.453		0.203
		0.48		*0.19*		*0.22*		*0.38*		*0.30*
6½	4	4.220	4	1.918	4	1.661	4	3.599	4	0.641
		4.86		*2.12*		*1.94*		*4.06*		*1.1*
7	3	4.813	3	1.949	3	2.015	3	3.964	3	0.849
		4.99		*2.15*		*1.98*		*4.12*		*1.1*

Figures in italics give the corresponding means for the Boston series.

TABLE XII

MEANS FOR MEASUREMENTS OF AREAS FROM ROENTGENOGRAMS OF GIRLS

AGE (YR.)	TOTAL LEG AREA		BONE AREA		MUSCLE AREA		BONE AND MUSCLE AREA		SKIN AND SUBCUTANEOUS TISSUE AREA	
	NUMBER OF CASES	MEAN (C.C.)	NUMBER OF CASES	MEAN (C.C.)	NUMBER OF CASES	MEAN (C.C.)	NUMBER OF CASES	MEAN (C.C.)	NUMBER OF CASES	MEAN (C.C.)
1	4	1.769	5	0.564	5	0.599	5	1.157	5	0.614
		2.11		*0.66*		*0.71*		*1.36*		*1.9*
1½										
2										
2½										
3	6	2.774	6	0.971	6	0.769	6	1.927	6	0.847
		3.35		*1.27*		*1.18*		*2.44*		*1.6*
3½										
4										
4½	2	3.346	2	1.270	2	1.315	2	2.585	2	0.761
		4.17		*1.64*		*1.55*		*3.18*		*1.5*
5	9	3.889	9	1.562	9	1.484	9	3.092	9	0.867
		4.34		*1.73*		*1.64*		*3.36*		*1.4*
5½	4	3.737	4	1.533	4	1.550	4	2.977	4	0.719
		4.58		*1.86*		*1.73*		*3.58*		*1.4*
6	24	4.300	24	1.759	24	1.683	24	3.442	24	0.858
		4.76		*1.94*		*1.82*		*3.75*		*1.4*
Sigma		0.462		0.195		0.209		0.351		0.182
		0.52		*0.21*		*0.22*		*0.41*		*0.22*
6½	3	4.183	3	1.775	3	1.636	3	3.412	3	0.771
		5.09		*2.08*		*1.97*		*4.03*		*1.3*

Figures in italics give the corresponding means of the Boston series.

was occasionally encountered, but this was usually attributed to a rachitic process observed also in the x-ray films.

The stage of osseous development, as revealed in roentgenograms of the hand and wrist, affords a basis for comparing the levels of anatomic development attained by the French children at each age with American norms. The Atlas prepared by Todd[11] and the chart prepared by Vogt and Vickers[12] were used to make this comparison.

OSSEOUS DEVELOPMENT OF HANDS AND WRISTS OF FRENCH CHILDREN BY X-RAY

I. CHILDREN ONE TO TEN YEARS INCLUSIVE, ACCORDING TO TODD'S STANDARDS

	BOYS		GIRLS	
Number of children studied	95		91	
Number retarded	74	(77.9%)	65	(71.4%)
Number of average development	2	(2.1%)	5	(5.5%)
Number advanced	19	(20.0%)	21	(23.1%)
Average retardation of retarded in months	13.7		11.8	
Average advancement of advanced in months	5.5		7.4	
Average excess of retardation over advancement per child in months	9.6		6.7	

II. CHILDREN ONE TO SEVEN YEARS INCLUSIVE, ACCORDING TO STANDARDS OF VOGT AND VICKERS

	BOYS		GIRLS	
Number of children studied	67		55	
Number retarded	36	(53.7%)	28	(50.9%)
Number of average development	18	(26.9%)	10	(18.2%)
Number advanced	13	(19.4%)	17	(30.9%)
Average retardation of retarded in months	18.6		13.2	
Average advancement of advanced in months	7.2		6.7	
Average excess of retardation over advancement per child in months	8.6		4.7	

Each x-ray film was assigned the osseous age of the standard picture which most nearly corresponded, or an age midway between two standard films if no film corresponded closely, when averaging all the features to be taken into account. Films of the hand and wrist of ninety-five boys and ninety-one girls, ranging in age from 1 to 10 years, were studied. For the purposes of these comparisons the age groups were more sharply restricted than for the study of measurements. A deviation of only one month from the birthday was allowed at 1 year, of two months from one through 6 years, and of three months thereafter. These films were compared with the standard pictures in Todd's *Atlas*, and the results are shown in Part I of Tables XIII and XIV. The same films for the children 1 to 7 years of age, that is, 67 boys and 55 girls, were compared with the Vogt and Vickers chart, and the results of this comparison are shown in Part II of these tables. It will be seen that by both methods of comparison there are many more retarded than ad-

vanced children and that the retarded deviate far more from the norms than do the advanced. Both of the American standards show the French boys to be more retarded than the girls, the Vogt and Vickers standards showing the greatest sex difference. The tables show that the Todd standards judge the average boy one month and the average girl two months more retarded than does the table of Vogt and Vickers. The latter, however, assigns greater retardation or advancement to those who deviate from the expected age.

Some of the children listed as either advanced or retarded in these tabulations do not differ from the expected pattern for age by more than six months or one step in the scale of standards and are, therefore, not in any sense unusual. The data have, therefore, been recalculated and only those children differing from the standards by more than six months have been counted. Furthermore, only children from 1 to 7 years of age have been included in order to make possible more direct comparison between the results obtained by using the two different standards. On this basis, there are 5 boys and 9 girls who are advanced according to Todd's norms and one boy and two girls according to the norms of Vogt and Vickers. On the same basis, 37 (55.2 per cent) boys and 25 (45.4 per cent) girls are retarded according to Todd, and 25 (37.3 per cent) boys and 20 (36.4 per cent) girls are retarded according to Vogt and Vickers. It should be recognized, however, that the norms used for these comparisons were based upon roentgenograms of children who had received more health service or who represented a higher socio-economic status than the children in the series studied in Marseilles.

It is the authors' opinion that there was far greater irregularity in the patterns of bone calcification among the Marseilles children than would be expected normally. If this opinion is correct, the retardation of the group should be considered in some measure, at least, due to environmental factors, even though there may be a fundamental racial difference in the general rate of bone maturation. There were not enough cases in each of the age groups to justify any conclusions as to the ages at which retardation and variability were most marked.

Numerous evidences of faulty bone structure or disturbed osseous formation were observed in studying the roentgenograms of the wrist and leg of the younger children. These were considered significant in view of the accompanying evidences of retarded growth during the first year, the subsequent short stature and tibial length, and the general irregularity and retardation of osseous development. They were understandable in view of the relatively small consumption of milk and lack of widespread use of vitamin D supplements to the diet in infancy. X-ray evidence of rickets was very common in infants under 2 years of age. Thirteen of 27 infants under 22 months, on whom satisfactory films were obtained, showed definite rickets, as interpreted both by the writers and by Dr. Astier, roentgenologist to the Hospital of the Conception in

TABLE XIII

RANKS FOR SELECTED MEASUREMENTS FROM ROENTGENOGRAMS OF BOYS MARSEILLES CHILDREN RELATED TO BOSTON NORMS

PART I

AGE (YR.)	LENGTH OF TIBIA					BREADTH OF MUSCLE					BREADTH OF SKIN AND SUBCUTANEOUS TISSUE				
	+	++	+++	++++	+++++	+	++	+++	++++	+++++	+	++	+++	++++	+++++
1	2	1				2		1		1		2	2		
1½	1		3	1			2	3				1	2	1	1
2															
2½		2	1					2	1				2	1	
3	3		2	1			1	4	1			2	4		
3½	2		1					3					3		
4	1	3	1					4				1	3	1	
4½	2		1					2	1			1	2		
5	2	2	1				2	3			1	2	2		
5½	3	1	1					5				1	4		
6	15	10	10			8	6	19	2			6	26	2	1
6½		1	3				1	3				1	2		
7	1	1	2					4					4		
Totals	32	21	26	2		10	12	53	5	1	1	17	56	5	2
Grand total	81					81					81				
Per cent	39.5	26	32	2.5		12	15	66	6	1	1	21	69	6	3

PART II

AGE (YR.)	BONE AREA					MUSCLE AREA					SKIN AND SUBCUTANEOUS TISSUE AREA				
	+	++	+++	++++	+++++	+	++	+++	++++	+++++	+	++	+++	++++	+++++
1	1		1			1		1				1	1		
1½	1	1	1			1	1	1			1	1	1		
2															
2½		1	2					3				1	2		
3		1	2	1				3		1		2	1		1
3½			2					2					2		
4	2	1	1				1					1	3		
4½		1	1				1		1			2			
5	1	1	2				2	2				3	1		
5½	1	1	2				2	2				2	2		
6	4	9	15	2		8	9	13			1	7	18	4	
6½			4				3	1				3	1		
7		2	1					3					3		
Totals	10	18	34	3		10	19	34	1	1	2	23	35	4	1
Grand total	65					65					65				
Per cent	15	28	52	5		15	29	52	2	2	3	35	54	6	2

TABLE XIV

RANKS FOR SELECTED MEASUREMENTS FROM ROENTGENOGRAMS OF GIRLS MARSEILLES CHILDREN RELATED TO BOSTON NORMS

PART I

AGE (YR.)	LENGTH OF TIBIA					BREADTH OF MUSCLE					BREADTH OF SKIN AND SUBCUTANEOUS TISSUE				
	+	++	+++	++++	+++++	+	++	+++	++++	+++++	+	++	+++	++++	+++++
1	3	4	2			3	1	3		2	2	1	5		1
1½	1	3						2		1			3		
2	2	1						3					1	2	
2½															
3	2	3	2			1		6			1	1	5		
3½	2		2					3		1			3	1	
4															
4½		1	1					2					2		
5	3	1	5				1	7	1			4	5		
5½	1		3				1	3				1	3		
6	9	10	6			1	2	17	4	1	5	6	13		1
6½	1		3				1	3			1	2	1		
7			2				1	1					2		
Totals	24	23	26			5	7	50	5	5	9	15	43	3	2
Grand total	73					72					72				
Per cent	33	31	36			7	10	69	7	7	12	21	60	4	3

PART II

AGE (YR.)	BONE AREA					MUSCLE AREA					SKIN AND SUBCUTANEOUS TISSUE AREA				
	+	++	+++	++++	+++++	+	++	+++	++++	+++++	+	++	+++	++++	+++++
1	1	2	2			2	1	1		1		2	3		
1½			1						1				1		
2		1						1					1		
2½															
3	3	2	1			1	2	3				4	1		1
3½		1						1				1			
4															
4½	1	1					2					1	1		
5		4	5				4	4	1			3	6		
5½	1	2	1			1	1	2				3	1		
6	1	9	13	1		3	4	16		1	3	8	12	1	
6½		2	1				2	1					3		
7			1					1				1			
Totals	7	24	25	1		7	16	30	2	2	3	23	29	1	1
Grand total	57					57					57				
Per cent	12	42	44	2		12	28	53	3.5	3.5	5	40	51	2	2

whose department these films were taken and who kindly rendered valuable assistance in making this study possible. In 9 of these 13 positive cases, the pediatrician recorded clinical evidences of rickets found on physical examination. When one considers that these infants were members of families chosen on a random sample basis from the city at large and did not represent a hospital or clinic population, this percentage incidence of a deficiency disease is impressive. There were, however, no advanced clinical cases in the group.

As these examinations were all made between February and June, it is probable that the mild positive cases would, in most instances, have undergone spontaneous healing before becoming markedly advanced, even if treatment had not been instituted. Very few evidences of rachitic deformities were found in the older children in this series, but there is no reason to believe that less rickets occurred among infants in previous years. Failure to provide a vitamin D supplement during infancy was not primarily a result of war but rather was due to lack of education of the public as to its importance for normal growth. The sunny climate of Marseilles and the low caloric diet customarily given infants probably prevented the occurrence of marked clinical cases.

Bands of differing densities in the postnatal areas of bone shadows, irregular bone trabeculations, dense lines of interrupted growth, and other indications of faulty or variable depositions of calcium were often seen at the younger ages, even when no signs characteristic of rickets were visible. Six infants out of 31 under 15 months of age (19.3 per cent) showed poor calcification of the bones. Of the three-year age group, three out of twelve (25 per cent) showed such disturbances. By six years of age this number had fallen to eight out of 61 (13 per cent) individuals. Thereafter, relatively few evidences of poor calcification were recognizable, other than the scars persisting well above the growth zones.

No x-ray or clinical evidences of scurvy were encountered in this series, despite the frequent finding of very low concentrations of ascorbic acid in the blood samples from these children.*

Taking into consideration both the faulty bone structure observed in the roentgenograms and the slightly lower positions held by some of the body measurements of infants under two years of age, as contrasted with those at later ages, there is the suggestion that nutritional factors may have caused some delay in growth during infancy and may, to some extent, explain the smaller size of French children as compared with American children. The possibility exists that the findings referred to among the infants born since the outbreak of the present war are due in part to recent dietary restrictions. However, as none of these infants or children have been re-examined to determine the rate at

*The blood studies made on these children will be reported later in connection with other tests for specific deficiencies and with analyses of dietary studies.

which they are growing, and as no data are available respecting the measurements or x-rays of the older children when they were infants, it is impossible to draw conclusions as to the period during which any adverse nutritional factors may have been operative. Further studies of these infants and children now being carried on at the "Institut de Récherches d'Hygiene" in Marseilles, both as to diets and as to increments of growth, should confirm or deny the reality of these age differences and throw more light on their causes.

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FURTHER STUDIES ON THE URINARY EXCRETION OF THIAMIN IN CHILDREN

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THIAMIN excretion in the urine has been used as an indication of thiamin tissue saturation and unsaturation. There are various degrees of tissue unsaturation. For practical purposes, two groups are considered: (1) tissue unsaturation with clinical signs or symptoms; (2) tissue unsaturation without clinical signs or symptoms. The latter group can be recognized only by laboratory means.

We have reported[1] on the urinary thiamin excretion of "healthy" children from 4 to 11 years of age who were hospitalized and so could be kept under close observation. These children were free to eat what they wished of the routine hospital diet. Their daily thiamin intake was found to average 990 μg, and it was significant that each child constantly approximated that figure. The thiamin excretion for the group averaged 268 μg per day. The lowest daily excretion for any child was found to be more than 100 μg. The average excretion was 27.2 per cent of the thiamin ingested in the diet. The figures for each child in this "healthy" group are given in Table I. No child excreted less than 20 per cent of the thiamin intake.

A study of ill children (acute, chronic, and convalescent) was then undertaken. The results were compared to and interpreted with those of the healthy children. The factors which operate to produce low urinary excretions were further studied.

Each patient was hospitalized and observed for from ten days to two months. Each child received a careful study, including history, physical examination, and indicated laboratory examinations. The daily dietary intake of carbohydrate, protein, fat, total calories and thiamin[2] was computed, and the daily urinary thiamin excretion was determined by a thiochrome[3] method. Fifty-five children received test doses in an attempt to find a serviceable saturation test.

RESULTS

In Table II will be found the results of our study of seventy-five children with various illnesses. In the acute diseases the first ten days after the temperature has returned to normal has been designated as early convalescence. The succeeding ten days have been designated as late convalescence. As long as the sedimentation rate is increased, rheumatic heart disease has been considered active. It has been con-

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sidered inactive when the sedimentation rate becomes normal. The other terms used in the table are self-explanatory.

Although the thiamin intakes were fairly high in all the early convalescent cases of pneumonia, the thiamin excretions were less than 80 μg. The excretions were 10 per cent or less of the thiamin ingested in all instances. All but one of the late convalescent cases of pneumonia had a thiamin excretion of more than 100 μg. Only three of these children excreted 20 per cent of the thiamin intake; all the others excreted 15 per cent or less.

TABLE I

HEALTHY CHILDREN

NAME	AGE (YR.)	SEX	WT. (LB.)	AVERAGE CALORIC INTAKE	AVERAGE B_1 INTAKE (μG)	AVERAGE B_1 OUTPUT (μG)	NUMBER OF DETERMINATIONS	$\frac{B_1 \text{ OUTPUT}^*}{B_1 \text{ INTAKE}}$ (%)
E. T.	4	F	37	1,986	999	193	27	20
E. D.	5	F	50	2,050	942	266	19	28
R. T.	6	F	51	2,106	990	279	25	28
S. B.	7	F	57	2,048	981	239	15	24
Q. C.	7	F	57	2,290	1,005	273	28	27
D. C.	7	F	60	2,159	990	301	29	30
J. D.	7	F	60	2,280	1,017	253	29	25
J. O.	7	M	54	1,910	858	305	18	36
B. B.	8	F	59	2,193	1,020	279	26	27
J. K.	8	F	61	2,140	972	254	15	26
L. M.	8	F	58	2,127	990	209	15	21
M. M.	8	F	57	2,104	999	214	15	21
P. F.	9	M	66	2,025	930	200	10	22
S. G.	9	F	86	2,221	1,059	300	25	28
C. M.	9	F	68	2,100	969	376	19	39
A. P.	9	F	74	2,250	1,017	263	29	26
N. S.	9	F	64	2,183	990	231	19	23
R. V.	9	F	77	2,217	1,017	359	29	35
R. C.	10	F	74	2,450	1,047	364	26	35
E. H.	10	F	83	2,239	1,014	289	29	28
J. L.	10	F	69	2,201	1,020	245	15	24
M. O'D.	10	F	68	2,198	1,002	204	39	20

*The percentage of the dietary thiamin intake that is excreted in the urine.

In the rheumatic heart disease group, the inactive cases excreted over 20 per cent of the thiamin intake. The active ones excreted less than 20 per cent, although many had a daily excretion of more than 100 μg.

The children with common colds (simple coryza) had a good excretion, 25 per cent or more of the intake. Those with severe upper respiratory infections and acute bronchitis excreted 15 per cent or less. In all the other various acute and early convalescent cases there was less than 20 per cent excretion of the ingested thiamin. Among the children with chronic conditions there were wide variations in the thiamin outputs and in the percentages of the intake which were excreted. Some excreted well over 100 μg and 20 per cent of the intake while others excreted less.

The results may be interpreted by examining the factors that influence urinary thiamin excretion: (1) the amount of thiamin ingested; (2) the body metabolism; (3) the amount of thiamin absorbed in the in-

testines; (4) the quantity of urine and the kidney function; (5) combination of several or all of these factors.

Amount Ingested.—The thiamin intake is the single most important factor influencing the urinary thiamin output. We have reported that healthy children, when permitted to choose freely from the hospital dietary, ingest an average of 990 μg of thiamin per day, or 45 μg per 100 calories. These children gained weight and were in excellent condition. Thus their thiamin intake would seem to have been adequate. However, we cannot say that this intake is the optimal amount, for these healthy children might have been better with an increased thiamin intake. The optimal intake is that which will best contribute to maximal health, growth, and development.

In the outpatient department we have been questioning parents concerning their children's diet. All these families are poor and many are ignorant of the proper composition of a diet. If one can rely on their statements and attempts to check roughly their diets, the majority have a thiamin intake which is only a bit lower than the healthy children on the hospital diet. The small minority who have a low thiamin intake fall into two groups. One group of children do not get enough to eat quantitatively and so have too little of all the necessary protective elements including thiamin. The other group comprises the children whose diet is so qualitatively constructed that the thiamin intake is low.

Even in this minority, who have a low thiamin intake, clinical thiamin deficiency (tissue unsaturation with clinical signs or symptoms) is so rare as to be almost nonexistent. "Subclinical" deficiency (tissue unsaturation without clinical signs or symptoms) is common as adduced from the urinary thiamin excretions thus far reported.

A study of ill children (Table II) reveals that those with acute diseases have a low thiamin intake during the febrile phase. In early and in late convalescence many of the children had not yet reached the thiamin intake which we have observed in the healthy child. In the main, the chronically ill child's thiamin intake was not as high as that in the healthy child.

Body Metabolism.—In all cases with infection and fever, there is an increased body metabolism and increased thiamin requirement. This factor is partly responsible for the low urinary thiamin in many of the acute cases tabulated. M. M., the hyperthyroid case, demonstrates the pure effect of increased metabolism. Before iodine therapy, with a basal metabolic rate of +25, the average thiamin output was 90 μg, or 13 per cent of the intake. After iodine therapy, with a basal metabolic rate of +7, the thiamin output was 253 μg, or 29 per cent of the intake. Then during an upper respiratory infection, the output fell to 141 μg and 15 per cent of the intake.

The Amount Absorbed.—It is possible that there is a defective absorption due to gastrointestinal dysfunction in many of these ill children.

This would be a contributory factor in producing low thiamin excretion. Individuals with diarrhea and postoperative patients are said to have a poor absorption. This phase requires further study and at present no figures can be given.

Quantity of Urine and Kidney Function.—These factors are important, but unfortunately little is known of their exact role. In the febrile diseases, fluids are forced. It is thought that prolonged increased fluid intake "washes" out the tissue thiamin and leads to unsaturation.

In cardiac decompensation, there may be a low thiamin excretion when there is a small quantity of urine. In obstructive kidney disease and nephritis, there may be thiamin retention with a low thiamin output. This does not necessarily indicate body unsaturation. We have seen two cases of nephrosis where the injection of large doses of thiamin seemed to promote a prolonged diuresis. We are unable to explain this and it may have been pure coincidence.

Combination of Factors.—In ill children the several factors will be found to operate in combination to produce low thiamin excretions. The effect of one, usually the amount of thiamin ingested, will be predominant, the others contributory.

Influence of Sulfathiazole on Thiamin Excretion.—Since sulfathiazole has been used in the treatment of many of the acutely ill children, it is important to know its effect on thiamin excretion. Four healthy children were observed for a week. The thiamin intake was computed and daily determinations of urinary thiamin were done. The following week, under the same conditions, sulfathiazole (0.2 Gm. per kilogram) was given daily. There was no significant difference between average thiamin excretions before, during, and following sulfathiazole administration.

Types of Saturation Tests.—Saturation tests have been based on measuring the thiamin excreted in the urine following the ingestion or injection of "test doses" of thiamin chloride. The large test dose is not sensitive in indicating the cases which have a slight or moderate degree of tissue unsaturation. Those with a marked degree of thiamin unsaturation are rare, and if laboratory confirmation is needed, either daily urinary determinations or a saturation test can be done. In the cases with slight unsaturation, the small test doses used thus far have not provided the desired information in all cases. In Table III are found the results with various smaller test doses, given intravenously and orally. The average daily excretion was always ascertained before giving the test dose. The results are variable and inconsistent, and we are unable to interpret them other than that they are unsatisfactory. The desirability of a quick and reliable saturation test is apparent and should be found if possible. At present, we feel that the most valuable information is obtained by determining the percentage of the dietary thiamin intake which is excreted in the urine.

TABLE II

ILL CHILDREN

NAME	DIAGNOSIS	AGE YR.	SEX	WT. (LB.)	AVERAGE CALORIC INTAKE	AVERAGE B_1 INTAKE (μG)	AVERAGE B_1 OUTPUT (μG)	NUMBER OF DETERMINATIONS	$\frac{B_1 \text{ OUTPUT}^*}{B_1 \text{ INTAKE}}$ (%)
C. I.	Pneumonia Early convalescent	4	M	30	1,922	861	64	8	7.4
D. H.	Pneumonia Early convalescent	6	F	43	1,618	735	55	9	7.4
A. A.	Lobar pneumonia Early convalescent	6	F	50	1,586	720	45	7	6.2
M. F.	Pneumonia Early convalescent	7	M	57	1,944	840	62	6	7.4
J. V.	Pneumonia Late convalescent	4	M	38	2,177	993	123	8	12.4
M. F.	Pneumonia Late convalescent	4	F	32	2,495	1,083	230	5	21.3
V. S.	Pneumonia Early convalescent Late convalescent	5	M	42	2,109 1,756	876 753	69 98	3 3	7.9 12.9
R. G.	Pneumonia Early convalescent Late convalescent	9	F	55	1,507 1,968	675 906	30 78	5 5	4.4 8.6
L. B.	Pneumonia Early convalescent Late convalescent	6	M	51	1,780 2,081	768 939	79 193	6 3	10.3 20.6

V. B.	Pneumonia								
	Early convalescent	10	F	57	1,874	732	47	3	6.4
	Late convalescent				1,961	852	102	8	12.0
E. R.	Pneumonia								
	Early convalescent	7	F	43	1,800	773	53	3	6.9
	Late convalescent				1,848	768	120	3	15.7
F. C.	Pneumonia								
	Early convalescent	7	M	48	2,568	1,011	77	3	7.6
	Late convalescent				2,568	1,107	156	6	14.2
R. H.	Lobar pneumonia								
	Early convalescent	6	M	43	1,938	900	61	3	6.8
	Late convalescent				1,782	795	202	6	25.4
T. M.	Lobar pneumonia								
	Early convalescent	7	M	43	1,651	711	76	4	10.7
	Late convalescent				2,161	897	117	4	13.0
D. Y.	Acute rheumatic fever	6	F	40	1,586	651	30	5	4.6
H. V.	Acute rheumatic fever								
	Early convalescent	3	F	32	1,481	593	100	3	16.8
J. S.	Acute rheumatic fever								
	Early convalescent	12	M	72	2,154	963	54	3	5.7
	Late convalescent				2,265	936	276	8	29.5
M. L.	Acute rheumatic fever								
	Late convalescent	9	M	55	1,737	750	104	4	13.9
R. N.	Rheumatic Heart Disease								
	Active	10	F	74	1,743	795	127	3	16.0
	Inactive				1,656	765	240	4	31.1

*The percentage of the dietary thiamin intake that is excreted in the urine.

TABLE II—CONT'D

NAME	DIAGNOSIS	AGE YR.	SEX	WT. (LB.)	AVERAGE CALORIC INTAKE	AVERAGE B_1 INTAKE (μG)	AVERAGE B_1 OUTPUT (μG)	NUMBER OF DETERMINATIONS	$\frac{B_1 \text{ OUTPUT}^*}{B_1 \text{ INTAKE}}$ (%)
L. F.	Rheumatic heart disease								
	Active	9	M	54	2,048	948	153	5	16.1
	Inactive				2,013	828	259	8	31.3
G. C.	Rheumatic heart disease								
	Active	8	M	51	1,748	771	87	8	11.2
	Inactive				2,037	951	327	3	34.4
J. G.	Rheumatic Heart Disease								
	Active	10	F	85	1,916	746	59	3	7.9
	Inactive				2,227	1,011	161	4	15.9
P. M.	Rheumatic heart disease								
	Active	9	M	50	2,059	882	110	8	12.5
L. M.	Rheumatic heart disease								
	Active	9	F	60	827	384	48	9	13.0
R. N.	Rheumatic heart disease								
	Active	11	F	69	1,527	618	75	8	12.0
P. C.	Rheumatic heart disease								
	Active	7	M	56	1,647	705	120	8	17.0
N. H.	Rheumatic heart disease								
	Active	10	M	62	1,144	495	81	3	16.4
W. G.	Rheumatic heart disease								
	Active	13	M	84	1,781	771	175	7	22.6

E. V.	Rheumatic heart disease Active	13	F	85	1,945	981	66	4	6.7
G. Y.	Rheumatic heart disease Active	10	F	70	1,916	912	156	6	17.1
J. K.	Rheumatic heart disease Inactive	10	F	72	1,625	681	355	3	52.0
J. H.	Rheumatic heart disease Inactive	5	F	42	1,512	666	242	5	36.2
A. H.	Rheumatic heart disease Inactive	8	F	56	1,985	837	130	8	15.5
B. S.	Rheumatic heart disease Inactive	8	F	58	1,901	774	179	8	23.2
M. C.	Chorea	8	F	62	2,109	1,008	89	4	8.9
E. R.	Chorea	9	F	66	2,132	933	221	10	24.0
M. M.	Chorea	5	F	45	2,173	942	159	9	17.0
F. G.	Common cold	9	F	64	1,919	870	223	11	25.6
V. B.	Common cold	8	F	58	1,984	861	228	6	26.4
R. C.	Common cold	4	M	36	1,286	615	159	6	25.9
F. T.	Nonspecific cervical adenopathy	11	M	97	2,514	1,092	333	9	30.6
W. B.	Vincent's angina	7	M	50	1,947	795	139	4	17.5
J. F.	Upper respiratory infection	5	F	46	2,000	882	138	8	15.7
V. F.	Upper respiratory infection	2	M	30	2,302	954	131	3	13.8

*The percentage of the dietary thiamin intake that is excreted in the urine.

TABLE II—CONT'D

NAME	DIAGNOSIS	AGE YR.	SEX	WT. (LB.)	AVERAGE CALORIC INTAKE	AVERAGE B_1 INTAKE (μG)	AVERAGE B_1 OUTPUT (μG)	NUMBER OF DETERMINATIONS	$\frac{B_1 \text{ OUTPUT}^*}{B_1 \text{ INTAKE}}$ (%)
J. McC.	Upper respiratory infection	5	M	48	1,457	669	73	5	10.8
F. G.	Upper respiratory infection	5	F	45	2,015	813	90	5	11.1
C. R.	Upper respiratory infection	9	F	74	1,859	726	108	6	14.8
G. B.	Acute bronchitis	5	F	52	1,911	807	90	7	11.1
E. L.	Allergic bronchitis	9	F	72	1,813	807	136	5	16.9
G. M.	Allergic bronchitis	7	M	46	2,064	900	149	8	16.6
C. LaR.	Measles Convalescent	7	F	54	2,171	882	168	7	19.0
M. J.	Measles encephalitis Early convalescent	6	F	48	1,822	840	91	11	10.8
J. McD.	Ruptured appendix, acute generalized peritonitis	8	M	51	164	135	6	6	4.4
L. O.	Postappendectomy Early convalescent	7	F	52	1,782	837	49	4	5.9
M. C.	Erysipelas of leg	6	F	51	1,954	870	63	8	7.2
J. G.	Acute osteomyelitis of femur	7	F	54	1,380	500	70	3	14.0
J. G.	Acute osteomyelitis of femur Convalescent	11	M	65	1,946 2,124	924 903	30 128	3 5	3.0 14.0
H. M.	Chronic lung abscess	13	F	80	2,634	831	136	6	16.0

L. J.	T.B., pleurisy, and peritonitis	7	M	47	1,713	690	55	8	8.0
I. C.	Food poisoning	4	F	36	1,879	795	127	5	16.0
C. F.	Malnutrition	6	M	33	1,288	522	89	3	17.0
E. D.	Congenital heart disease	7	M	56	1,722	774	148	12	19.2
G. E.	Congenital heart disease	8	F	49	1,595	663	214	6	32.0
J. M.	Hypertension Etiology?	11	M	76	2,029	879	239	6	26.9
E. R.	Lues	8	F	43	1,767	741	135	7	18.1
M. L.	Dystonia musculorum deformans	8	M	56	1,634	774	138	12	17.8
R. C.	Epilepsy	7	M	74	2,155	1,047	110	3	10.4
C. P.	Little's disease	4	M	33	1,801	774	132	8	17.1
W. C.	Hemophilia	8	M	58	1,582	750	207	5	27.5
D. B.	Idiopathic purpura	7	F	60	2,273	1,038	206	7	19.8
T. A.	Tumor of eye	5	M	51	2,041	819	196	3	23.9
R. F.	Ascariasis trichuriasis	8	M	54	2,318	975	230	11	23.6
E. C.	Ulcerative colitis	9	F	49	1,365	531	54	10	10.0
F. J.	Chronic nephritis	8	M	64	974	396	36	8	9.0
M. M	Hyperthyroidism								
	Before iodine therapy	7	F	46	1,683	714	90	9	13.0
	After iodine therapy				1,991	840	253	20	29.0
	During upper respiratory infection				2,019	933	141	8	15.0

*The percentage of the dietary thiamin intake that is excreted in the urine.

TABLE III

TEST DOSES

NAME	AGE (YR.)	WT. (LB.)	METHOD OF ADMINISTRATION	TEST DOSE (MG.)	AVERAGE DAILY EXCRETION BEFORE TEST DOSE (μG)	EXCRETION AFTER TEST DOSE (μG)	PER CENT OF TEST DOSE EXCRETED
G. E.	8	49	I.V.	0.5	214	148	--
H. M.	13	80	I.V.	0.5	136	305	27
J. G.	11	65	I.V.	0.5	128	333	41
E. R.	9	66	I.V.	0.5	221	478	51
M. M.	5	45	I.V.	0.5	159	666	102
L. M.	9	60	I.V.	1.0	48	94	5
P. C.	7	56	I.V.	1.0	120	531	41
R. N.	11	69	I.V.	1.0	75	495	42
T. M.	7	43	I.V.	1.0	117	547	43
P. M.	9	50	I.V.	1.0	110	556	45
L. O.	7	52	I.V.	1.0	49	642	49
R. F.	8	54	I.V.	1.0	230	909	68
D. Y.	6	40	Oral	1.0	30	126	10
L. J.	7	47	Oral	1.0	55	160	11
A. H.	8	56	Oral	1.0	130	251	12
M. D. C.	6	51	Oral	1.0	63	197	13
J. G.	10	85	Oral	1.0	161	355	13
A. A.	6	50	Oral	1.0	45	178	19
F. T.	11	97	Oral	1.0	333	575	26
E. R.	8	43	Oral	1.5	135	271	9
G. B.	5	52	Oral	2.0	90	152	5
L. F.	9	54	Oral	2.0	259	450	10
L. F.	9	54	Oral	2.0	153	595	22
F. G.	9	64	Oral	2.5	223	560	13
C. R.	9	74	Oral	2.5?	108	530	17
W. G.	13	84	Oral	3.0	175	326	5
C. I.	4	40	Oral	3.0	64	240	6
J. K.	10	72	Oral	3.0	355	669	10
E. V.	13	85	Oral	3.0	79	406	11
J. H.	5	42	Oral	3.0	242	691	15
C. LaR.	7	54	Oral	3.0	168	660	16
M. L.	9	55	Oral	3.0	104	638	18
R. N.	10	74	Oral	3.0	240	803	19
M. C.	8	62	Oral	3.0	418	1,075	22
D. H.	6	43	Oral	3.0 (1.0 t.i.d.)	55	136	3
J. Mc.	5	48	Oral	3.0 (1.0 t.i.d.)	73	197	4
E. R.	7	43	Oral	3.0 (1.0 t.i.d.)	120	303	6
J. S.	12	72	Oral	3.0 (1.0 t.i.d.)	276	538	9
T. A.	5	51	Oral	3.0 (1.0 t.i.d.)	196	494	10
V. B.	8	58	Oral	3.0 (1.0 t.i.d.)	102	397	10
J. F.	5	46	Oral	3.0 (1.0 t.i.d.)	138	471	11
R. G.	9	55	Oral	3.0 (1.0 t.i.d.)	78	400	11
V. B.	8	58	Oral	3.0 (1.0 t.i.d.)	228	605	13
J. G.	7	54	Oral	3.0 (1.0 t.i.d.)	111	606	17
J. V.	4	38	Oral	3.0 (1.0 t.i.d.)	123	684	19
F. G.	5	45	Oral	3.0 (1.0 t.i.d.)	91	660	19
W. C.	8	58	Oral	3.0 (1.0 t.i.d.)	207	766	19
E. L.	9	72	Oral	3.0 (1.0 t.i.d.)	136	710	19
V. S.	5	42	Oral	3.0 (1.0 t.i.d.)	98	733	21
G. M.	7	46	Oral	3.0 (1.0 t.i.d.)	149	1,025	29
H. V.	3	32	Oral	3.0 (1.0 t.i.d.)	170	1,199	34
B. S.	8	58	Oral	3.0 (1.0 t.i.d.)	179	1,232	35
F. C.	7	48	Oral	3.0 (1.0 t.i.d.)	156	1,913	59

Indications for Thiamin Supplements Based on Laboratory Data.—In studying tissue saturation, a single day's estimation of the urinary thiamin does not offer as much information as an average of three days. The approximate amount of thiamin in the child's daily diet should be known. This is not difficult to compute if one has a chart of the common foods with the thiamin content in the usual portion. Then the percentage of the thiamin intake that is excreted can be determined. This really constitutes the best test dose, as there are no artificial conditions imposed.

A daily thiamin excretion of more than 100 μg is not in itself a satisfactory criterion of tissue saturation. We believe that tissue saturation is approached when the child excretes 20 per cent or more of the dietary thiamin intake.

On this basis, the diets of most of the acute and chronically ill children listed in Table II will have to be supplemented with thiamin for short periods to secure saturation. The acutely ill children will need supplementing for only one week or less during convalescence. The chronically ill may need additional thiamin for a longer period. It seems best to use a vitamin B complex preparation rather than thiamin chloride itself, for it is likely that there is an associated tissue unsaturation of the other individual members of the B complex.

SUMMARY AND CONCLUSIONS

1. Healthy children had an average intake of 990 μg of thiamin and excreted 27.2 per cent, or 268 μg, in the urine.

2. The factors which produced low thiamin excretions and tissue unsaturation have been discussed.

3. Saturation tests employing various test doses have not been satisfactory thus far. The best indication of tissue saturation or unsaturation is obtained by determining the percentage of the dietary thiamin intake excreted in the urine.

4. Children on an adequate diet (45 μg of thiamin per 100 calories) who excrete less than 20 per cent of the thiamin intake, require supplementing of the diet with thiamin to secure tissue saturation.

5. Children convalescing from acute illnesses and some children with chronic illnesses excrete less than 20 per cent of the thiamin intake in the urine. These children require thiamin supplementation for short periods.

We wish to thank Dr. Douglas Hennessy of Fordham University for his interest and help. We appreciate the assistance of Miss L. Stuart, Miss J. Mestern, and Miss G. Gilman.

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INTRACUTANEOUS IMMUNIZATION AGAINST SCARLET FEVER

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THE severe general systemic reactions which often follow the subcutaneous injection of scarlet fever streptococcus toxin have led many institutions and practicing physicians to reject this procedure of scarlet fever immunization.

Rappaport[1] attempted to reduce the number and severity of these reactions by giving more numerous injections of smaller doses. Friedman and co-workers[2] tried immunizing by means of nasal instillation of scarlet fever toxin. The inunction method was reported by Martmer[3] in 1932. In 1938 Dick and Dick[4] successfully immunized by the oral administration of scarlet fever toxin. A further attempt to reduce reactions by the use of formalized toxin was reported by Veldee[5] and Anderson.[6] The desire to devise a means of inoculating against scarlet fever in such a manner as to reduce the severity of the reactions led Robinson[7] and Kern and his associates[8] to follow the lead of Tuft[9] and utilize the skin as an organ to develop antibodies.

The purpose of our study was to convert a positive Dick reaction into a negative Dick reaction by the intracutaneous injection of scarlet fever toxin, to determine the duration of immunity so produced, to determine the minimum number of injections necessary, and to determine the interval between injections which gives the greatest immunity.

The patients studied were children from the Prophylaxis Clinic of the Children's Medical Service of Bellevue Hospital. All nationalities, races, and creeds from the lower east side of New York City were represented. The ages were from 6 months to 10 years. For comparison, a group of young adults (student nurses) were also studied. This study was started in 1937 and completed in 1941.

The material, scarlet fever streptococcus toxin,* was in five vials of graduated doses, namely, 500, 2,000, 8,000, and 25,000 skin test doses per cubic centimeter, and the fifth dilution contained 80,000 to 100,000 skin test doses in 2 c.c. The same toxin ordinarily used for subcutaneous injection was used.†

The procedure was as follows. Infants and children attending our clinic were given Dick tests and Dick control tests in the usual manner.

From the Prophylaxis Clinic of the Children's Medical Service, Bellevue Hospital, and the Department of Pediatrics, New York University College of Medicine.

This study was aided by a grant from the Lederle Laboratories.

*Prepared by the Lederle Laboratories and approved by the Scarlet Fever Committee.

†Dick and Dick control material was from Lederle Laboratories and the Department of Health of New York City.

The needles and syringes used were sterilized by boiling and never used for any other purpose. The tests were read in twenty-four hours. Any area of erythema, no matter how faint, which measured 10 mm. or more in its greatest diameter was considered positive.

Infants and children with positive Dick tests were given intracutaneous injections of 0.1 c.c. of scarlet fever toxin in the skin over the upper and outer aspect of the thigh. Alternate thighs were used for each injection, which was of a stronger dilution. The intervals between injections were two, three, and four weeks. The patients were immunized to the point of a negative skin test, and were then given subsequent Dick tests periodically for as long as four years.

Number of Injections.—Three general groupings of five, four, and three injections were used. Those who were given five injections received 50, 200, 800, 2,500, and 9,000 skin test doses, totaling 12,550. Most who were given four injections received 100, 400, 2,500, and 9,000 skin test doses, totaling 12,000. Some of those who received four injections were given 400, 2,500, 9,000, and 9,000 skin test doses, totaling 20,900. The group who received three injections had 400, 2,500, and 9,000 skin test doses, totaling 11,900.

Reactions.—All mothers were asked to note carefully any systemic reactions which occurred and also to measure roughly the area of local erythema which resulted from the injection. On subsequent visits to the clinic they reported their findings.

TABLE I

AGE AND SEX DISTRIBUTION

AGE AT TIME OF INTRACUTANEOUS IMMUNIZATION	SEX	
	FEMALE	MALE
6 to 12 months	3	1
12 to 18 months	22	9
18 to 24 months	22	18
2 to 3 years	19	10
3 to 4 years	18	9
4 to 5 years	7	7
5 to 6 years	13	6
6 to 7 years	4	2
7 to 8 years	2	2
8 to 9 years	3	3
9 to 10 years	2	2
10 years and over	2	0
Totals	117	70

CLINICAL STUDY

Two hundred and eighty-three patients were actively immunized against scarlet fever. Of these, 250 infants and children were immunized intracutaneously with the procedure outlined. Of this number, a total of 187 infants and children were followed completely for a sufficient length of time so that accurate records of the course of their immunity

could be obtained. The age and sex distribution of the patients are listed in Table I. The majority were between the ages of 1 and 5 years. Seventy-two children received five or more injections; 78 received four injections, and 37 received three injections. The average number of skin test doses with details may be found in Table II.

All of the 187 children immunized received at least one follow-up Dick test, and 141 received two or more Dick retests.

TABLE II

CASES ACCORDING TO NUMBER OF INJECTIONS AND AVERAGE NUMBER OF SKIN TEST DOSES

ORIGINAL NUMBER OF INJECTIONS	NUMBER OF CASES	AVERAGE NUMBER OF SKIN TEST DOSES
5	72	12,847*
4	78	14,067†
3	37	11,808‡

*Of those receiving five injections, 58 received 12,550 skin test doses, eight received between 12,750 and 15,050 skin test doses, 4 less than 12,550, 2 more than 15,050.

†Of those receiving four injections, 54 received 12,000 skin test doses, 18 between 20,900 and 21,300 skin test doses, 3 received 14,000 skin test doses, 3 between 12,300 and 13,150 skin test doses.

‡Of those receiving three injections, 30 received 11,900 skin test doses, 5 under 11,900 skin test doses, 2 more than 11,900 skin test doses.

RESULTS

Table III represents the composite results of all the Dick retests which were given from one month to four years after the last injection of scarlet fever toxin. Of the 187 children immunized, 144 returned within three months for their first Dick retest, while the remaining 43 had their first retest three to eighteen months after the last injection.

There was a total of 100 (69.4 per cent) negative reactors at the end of three months, divided as follows: five injections, 76.7 per cent negative; four injections, 68.4 per cent negative; three injections, 55.5 per cent negative. Of the 33 retested after three to six months, 26 (78.8 per cent) reacted negatively. There were twenty-four patients who on the first retest had positive Dick reactions. They were given an additional injection of 9,000 skin test doses. Seven of them were retested three months later and 6 of them reacted negatively.

REACTIONS

The local reaction resulting from the intracutaneous injection of scarlet fever toxin was an area of erythema measuring from a minimum of 12 mm. to a maximum of 100 mm. in its greatest diameter. The height of the reaction was usually reached in twenty-four to forty-eight hours and then rapidly subsided. However, some areas of pigmentation and desquamation were noted seven to ten days after the injection.

In Table IV we have tabulated both the systemic reactions of the entire tested group and the reactions which follow each separate injection. We have arbitrarily divided the reactions into severe, moderate, and mild,

TABLE III

COMPOSITE RESULTS OF DICK RETESTS AFTER IMMUNIZATION

TOTAL NUMBER OF INJECTIONS	INTERVAL BETWEEN LAST INJECTION AND DICK RETEST													
	1 TO 3 MO.		3 TO 6 MO.		6 TO 9 MO.		9 TO 12 MO.		12 TO 18 MO.		18 TO 24 MO.		24 MO. +	
	NEG.	POS.	NEG.	POS.	NEG.	POS.	NEG.	POS.	NEG.	POS.	NEG.	POS.	NEG.	POS.
5	46 76.7%	14 23.3%	14 87.5%	2 12.5%	13 76.5%	4 23.5%	9 81.9%	2 18.1%	13 81.3%	3 18.7%	6 50.0%	6 50.0%	20 100%	0 0%
4	39 68.4%	18 31.6%	9 71.5%	4 28.5%	11 52.4%	10 47.6%	8 57.1%	6 42.9%	16 84.2%	3 15.8%	10 90.9%	1 9.1%	13 100%	0 0%
3	15 55.5%	12 44.5%	3 75.0%	1 25.0%	1 100.0%	0 0%	1 33.3%	2 66.7%	3 100.0%	0 0%	5 100.0%	0 0%	4 100%	0 0%
Case Total % Total	100 69.4%	44 30.6%	26 78.8%	7 22.2%	25 64.1%	14 35.9%	18 64.3%	10 35.7%	32 84.2%	6 15.8%	21 75.0%	7 25.0%	37 100%	0 0%

according to the criteria found in the table. A child with any complaint, regardless of its nature (i.e., pain or itching at site of injection), was considered a reactor.

TABLE IV

SYSTEMIC REACTIONS FOLLOWING INTRACUTANEOUS IMMUNIZATION

REACTION	MANIFESTATIONS	NUMBER OF CASES	PER CENT	NUMBER OF INJECTIONS	PER CENT
Severe	Urticarial wheals; edema of face; rash; high fever	5	2.7	9	1.0
Moderate	Moderate temperature up to 102° F. rectally; vomiting night of injection	12	6.4	14	1.7
Mild	Slight fever, 100° F. rectally; cranky; restless; vomiting; itching; irritable; anorexia; malaise; pain, site of injection	36	19.2	122	13.9
None		134	71.7	730	83.4
Totals		187	100.0	875	100.0

Studying this table, we note that 5 children had a total of nine severe reactions. Four of these 5 children developed immediate urticarial wheals and edema in from fifteen minutes to two hours after the injection. The reactions followed the larger doses of toxin. Two of these patients had two such reactions. Three children had scarlatinaform rashes within twenty-four hours after the injection. Two of the 5 patients had both urticarial wheals and a scarlatinaform rash. Following the initial severe reaction, each subsequent injection was accompanied by a 3-minim dose of adrenalin, which prevented the occurrence of these untoward symptoms.

Twelve of the 187 children who received scarlet fever immunization intracutaneously had fourteen moderate reactions. Of these 12, 10 had only one reaction while 2 had two such reactions.

Thirty-six children had 122 mild reactions. In this group it is apparent that those who had vague complaints of irritability and restlessness the night of the injection, or itching, soreness, or pain at the site of injection had these same complaints with every injection.

Of these 187 children injected, 134 (71.7 per cent) had no reactions. In all, 875 injections were administered, and of these, 730 (83.4 per cent) were followed by no reaction.

Many physicians who immunize against scarlet fever by the subcutaneous method of injection have emphasized the fact that reactions have been markedly reduced by graduating the injection dosages in direct relationship to the size of the original Dick test. They feel that the larger the Dick test, the smaller the original dose of scarlet fever toxin should be, with a gradual increase in the subsequent number of skin test doses administered.

Table V tabulates the systemic reactions obtained in relationship to the original Dick test. The size of the test did not influence our dosages, and a study of this table reveals that no definite relationship exists. Four of our severe reactions occurred in patients having the smallest Dick tests. However, a proportional comparison of our mild reactors shows a small increase in the number of reactors as the size of the original Dick increases.

TABLE V

RELATION OF ORIGINAL DICK TEST TO SYSTEMIC REACTIONS

ORIGINAL DICK REACTION	TOTAL NUMBER OF CASES	SEVERE		MODERATE		MILD		NONE	
		NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT
10 to 20 mm.	107	4	3.7	8	7.5	17	15.9	78	72.9
20 to 30 mm.	51	1	1.9	0	0	11	21.6	39	76.5
30 to 40 mm.	27	0	0	4	14.8	8	29.7	15	55.5
40 to 50 mm.	2	0	0	0	0	0	0	2	100
Totals	187	5	2.7	12	6.4	36	19.2	134	71.7

To our knowledge no case of scarlet fever developed in any of our patients. One boy, aged 2 years, who was immunized by the five-dose method, receiving a total of 12,550 skin test doses of scarlet fever toxin intracutaneously, ten months after the last injection and two weeks after a negative Dick retest, was seen at the clinic with a history of high fever, vomiting, and an erythematous rash. No history of scarlet fever contact could be obtained. On physical examination the child had a rectal temperature of 102° F. and a typical punctate scarlatinaform rash over the entire body, particularly marked around neck, axilla, and groin. A diagnosis of scarlet fever was made, and the boy was hospitalized at Willard Parker. A Schultz-Carlton test performed was negative. On the following day the temperature was normal and the rash had completely faded. He was discharged after one day of hospitalization with the diagnosis of toxic erythema. A Dick test performed after the disappearance of the rash was also negative.

Duration of Immunity.—All of the 37 children we were able to Dick test from two to four years after the last injection reacted negatively. Of 14 children who received one added injection of 9,000 skin test doses and who were retested in two to four years following this injection, 13 reacted negatively. In all of these 51 patients tested, 50, or 98.1 per cent, were Dick negative. There was no relationship between age or sex of our patients and the results of their Dick tests. There were 9 males and 31 females; 18 were under 2 years of age and 27 under 3 years of age.

DISCUSSION

Our study shows that the local and systemic reactions can be reduced to a minimum by the intracutaneous method of immunization against scarlet fever, using only one-tenth of the amount usually injected sub-

cutaneously. The conversion of a Dick positive to a Dick negative reactor is based upon three factors: the total number of skin test doses, the number of injections, and the interval between the injections. Our best results were in those who received five injections, with an interval of three or more weeks between each injection, regardless of the total number of skin test doses administered. Our next best results were in the group who received five injections with an interval of one to two weeks between each injection. Thus we may conclude that in scarlet fever immunization as well as in diphtheria, tetanus, and typhoid immunization, the best antibody response results from the greatest number of injections over a prolonged period of time.

Kern and co-workers,[10] reporting on forty cases retested six months after intracutaneous immunization against scarlet fever, found 40 per cent negative Dick reactors. However, the total number of skin test doses was only 4,575. Fisher and Van Gelder[11] reported 100 per cent reversal of the Dick reactions at the end of three months with the intracutaneous method of immunization in the 120 cases they studied. In spite of the fact that our patients received an equal or greater amount of skin test doses and injections, we found only 69.4 per cent negative Dick tests at the end of three months in the 187 children we immunized. We cannot explain this difference except on the basis of a possible variation in the potency of the materials used, and the fact that they considered those with positive Dick tests and positive controls as negative. Of the 187 patients immunized, 88 (47 per cent) lost their immunity within two years. Sixty-six of these positive reactors received an additional injection of 9,000 skin test doses; 18 of these (27.2 per cent) remained Dick positive. These results are not as favorable as those obtained by Bacon,[12] who found that by the subcutaneous method of immunization that only 9 of 59 patients (18 per cent) were Dick positive at the end of two and a half years. However, we were able to follow 51 patients for a period exceeding two years and as long as four years after immunization and found that 50 of these remained Dick negative (98.1 per cent). Thus where immunity to scarlet fever is lost, it usually occurs within two years after the injection series has been completed.

By this intracutaneous method of immunization we were able to reduce systemic reactions to a great degree. Of the 187 children injected, 134 (71.7 per cent) had absolutely no reaction. Moreover, of the 875 immunizing injections given intracutaneously, 750 (83.5 per cent) were followed by no reaction. Fisher and Van Gelder had only 37 per cent of their cases free from reactions, probably because of the larger doses given by them.

We performed 481 Dick tests and noted 29 (6 per cent) positive Dick controls. These occurred in 20 children. Before or after this positive control reaction, each patient had one or more negative control tests.

For statistical purposes we disregarded these positive controls and merely tabulated the results of the Dick tests. It is also interesting to note that in 2 patients we obtained positive controls with negative Dick tests. Our figures are in marked contrast with Fisher and Van Gelder who reported 46 per cent positive controls in one group of 58 children and then 1.6 per cent positive controls in another group of 62 children. This discrepancy was not explained. The exact significance of a positive Dick control is unknown to us. Our positive Dick controls occurred without any relation to the time interval between the original injection or to the frequency of the subsequent Dick tests. The reaction to the control material is probably due to some acquired sensitivity from the injections, as no positive controls were obtained with the original Dick tests.

Careful investigation failed to show any relationship existing between allergy and the size of the original Dick test or between allergy and the severity of the local and systemic reactions.

We were desirous of learning if the color of the hair, as an index of skin pigmentation, could be correlated to the size of the original Dick test and the severity of the reactions which occurred from immunization. We arrived at no definite conclusions. In our series of patients studied, the blonde- and red-haired children did not react more violently than did those with black hair. Moreover, the brown-haired children had the largest Dick tests and most severe reactions.

In our prophylaxis clinic, we often gave simultaneous injections against scarlet fever and diphtheria, pertussis, or smallpox. This procedure did not cause any increase in the number or severity of reactions and apparently did not effect the immunity.

For the purpose of comparison, we injected scarlet fever toxin subcutaneously in a small group of patients under identical conditions. With this group we found that 28 per cent had moderate or severe reactions compared with 9 per cent in the intracutaneous group. Moreover, only 7 per cent had no reaction compared with 71.6 per cent in the intracutaneous group.

We were also able to study a group of 23 student nurses from Bellevue Hospital who were immunized intracutaneously. Here we found a definite relationship between the size of the original Dick test and the local erythema following each immunizing injection. Moreover, the number and severity of our reactions were more marked in this older age group than in our children. At the end of three months, 81 per cent showed conversion to a negative Dick test and of these, at the end of nine months, 93 per cent were still negative. Those with negative Dick tests were subsequently sent to work on the scarlet fever wards at Willard Parker Hospital and none contracted the disease.

Incidentally, in the hundreds of children we have Dick-tested, it was noted that the negative Dick test of early infancy was spontaneously converted to positive between the eighteenth and twenty-fourth month of life.

SUMMARY AND CONCLUSIONS

1. One hundred eighty-seven infants and children were intracutaneously immunized with scarlet fever toxin and were retested at intervals of three months to four years.

2. Three general groupings of five, four, and three injections were used, averaging 12,847, 14,067, and 11,808 skin test doses, respectively.

3. Sixty-nine and four-tenths per cent of the patients Dick-tested three months after the last injection gave a negative reaction.

4. Of fifty-one patients tested two to four years after immunization, 98.1 per cent were Dick negative.

5. Where immunity to scarlet fever is lost, it is lost within two years after the immunizing series has been completed.

6. The five-injection group had the greatest percentage of conversions from Dick positive to Dick negative.

7. The number and severity of the reactions resulting from the intracutaneous method of immunization were less than those resulting from the subcutaneous method. Of 875 immunizing injections given intracutaneously, 83.4 per cent were followed by no reaction.

8. The reactions in younger age groups are milder and less frequent than with adults.

9. The "natural" immunity to scarlet fever of early infancy is lost between the eighteenth and twenty-fourth month of life.

10. It is of importance to note the economy of using one-tenth the amount of toxin ordinarily necessary to produce immunity to scarlet fever.

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RESISTANCE TO INFECTION AS AFFECTED BY VARIATIONS IN THE PROPORTIONS OF PROTEIN, FAT, AND CARBOHYDRATE IN THE DIET*

An Experimental Study

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MEDICAL literature contains numerous allusions to an increase in susceptibility to infection among persons whose environment, economic circumstances, or dietary habits have imposed a condition of malnutrition. However, experimental proof of a direct causal relationship between disturbances of nutrition and lowered resistance is amazingly deficient in many respects and very little is known regarding the physiologic and immunologic mechanisms concerned. This statement applies particularly to alleged relationships involving the primary food substances, protein, fat, and carbohydrate. The literature on this phase of the subject is surprisingly scanty and is difficult to analyze because of the many variables involved. In fact, most of the published reports on the subject are based upon empirical observations on the human subject in whom multiple instead of single dietary deficiencies are prone to occur.

For obvious reasons adequately controlled experiments involving the artificial production of infection and dietary deficiencies cannot be carried out on the human subject. It is necessary, therefore, to resort to animal experimentation to obtain reasonably accurate information. Experimental studies on the effects of vitamin deficiencies in animals have yielded valuable information. From such investigations it now appears to be fairly well established that a deficiency of either vitamin A or vitamin C lowers resistance to various acute infections.[1, 2] In all probability severe deficiencies involving members of the vitamin B complex, or even vitamin D, may have a similar though less striking effect. It is generally agreed, however, that an excess of vitamins in the diet does not increase resistance to infection in the nondeficient subject. Some of the reported results of animal experiments on the relationship of dietary protein, fat, and carbohydrate to resistance have been somewhat suggestive but not conclusive. For instance, Watson[3] found that young mice reared on separated milk and oatmeal were more resistant to infection with *B. typhi murium* than were similar animals fed a diet in which

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the milk was omitted and more oatmeal was given. Unfortunately, it is impossible to say from such experiments which of the several variables involved was the important one.

The experiments reported in the present communication were undertaken because of a widely recognized need for additional information regarding this latter phase of the subject. Pediatricians have long regarded the so-called "hydrolabile" child, who has been maintained on an excessively high carbohydrate diet, as being peculiarly susceptible to all types of acute infection. Since the protein intake of such patients is usually extremely low, this factor has been considered by some observers to be of primary importance. In the course of his extensive studies on fox encephalitis, Green[4] has repeatedly observed that foxes are rendered more susceptible to infection by use of diets deficient in protein. Sabin and Duffey[5] have found that general nutrition is an important factor in the development of constitutional barriers to involvement of the nervous system by viruses. Parents of children treated for epilepsy by means of the ketogenic diet, which is high in fat and low in carbohydrate, not infrequently volunteer the opinion that such children suffer little or not at all from the common upper respiratory infections when compared with other members of the immediate family subsisting on ordinary mixed diets.[6] Unfortunately, such empirical observations are too few and the conditions involved are too complex to justify an attempt to subject them to statistical analysis. The specific purpose of the investigation reported in this paper was to determine with greater certainty whether or not susceptibility to infection is influenced to any important degree by variations in the proportions of protein, fat, and carbohydrate in the diet.

METHODS AND MATERIALS USED

With this objective in view, young albino mice were inoculated subcutaneously with many times the lethal dose of virulent pneumococci after being maintained on one or other of a series of test diets for a period of six weeks. The following types of synthetic diet were carefully constructed to represent the three chief variations for each of the primary food substances:

S_1, Control or "normal" diet (medium protein, fat, and carbohydrate)
S_2, High carbohydrate, medium fat, low protein diet
S_3, High carbohydrate, medium protein, low fat diet
S_4, High protein, medium fat, low carbohydrate diet
S_5, High protein, medium carbohydrate, low fat diet
S_6, High fat, medium carbohydrate, low protein diet
S_7, High fat, medium protein, low carbohydrate diet

The exact compositions of the diets are shown in detail in Table I. The added minerals and vitamins were kept constant and were the same in all of the diets. An additional control group of animals was subjected

to the same test after being maintained on a commercial animal food mixture, Purina dog chow, for six weeks.

The fibrin used as the chief source of protein was prepared from fresh, crude, beef blood fibrin, which was first passed through a fine meshed meat grinder and then washed with running cold tap water for twenty-four hours. When decolorization was complete, it was washed with distilled water and finally extracted with cold 95 per cent ethyl alcohol for twenty-four hours before being dried. This process removed most of the minerals and lipids. Carbohydrate was given in the form of dextrinized tapioca. Lard, cod-liver oil (furnishing vitamins A and D), and beef tallow were used as sources of fat. Members of the vitamin B complex were furnished by a generous allowance of yeast powder. It was assumed that the mouse does not require extra vitamin C.

TABLE I

PERCENTAGE COMPOSITION OF EXPERIMENTAL SYNTHETIC DIETS*

	S_1	S_2	S_3	S_4	S_5	S_6	S_7
Fibrin	20.0	4.5	10.0	60.0	55.0	10.0	20.0
Dextrinized tapioca	50.0	76.5	78.0	15.0	33.0	30.0	20.0
Beef tallow	–	–	–	–	–	10.0	10.0
Lard	20.0	9.0	2.0	15.0	2.0	40.0	40.0
Cod-liver oil	3.0	3.0	3.0	3.0	3.0	3.0	3.0
Osborne-Mendel salt mixture	7.0	7.0	7.0	7.0	7.0	7.0	7.0
Per Cent by Weight							
Protein	20.0	4.5	10.0	60.0	55.0	10.0	20.0
Carbohydrate	50.0	76.5	78.0	15.0	33.0	30.0	20.0
Fat	23.0	12.0	5.0	18.0	5.0	53.0	53.0
Per Cent by Calories							
Protein	16.4	4.2	10.1	51.9	55.4	6.2	12.5
Carbohydrate	41.1	70.8	78.6	13.0	33.3	18.8	12.5
Fat	42.5	25.0	11.3	35.1	11.3	75.0	75.0
Caloric value per gram	4.87	4.32	3.97	4.62	3.97	6.37	6.37

*Mead's yeast powder, 200 mg. daily, was given in addition.

The groups of mice placed on the different test diets were uniform in breed, age, weight, and sex so far as this was possible of attainment. The animals were kept in individual cages provided with water bottles and waste-proof food cups. They were weighed regularly at intervals of three days to the nearest 0.5 Gm. While the temperature and humidity of the animal room were not kept constant, all mice were subjected to the same environmental conditions.

The particular strain of type II pneumococcus used was obtained through the courtesy of Dr. W. P. Larson and Dr. R. N. Bieter, who have employed it extensively in chemotherapeutic studies carried out on mice during the past two years.[7] It was originally isolated from a human case of lobar pneumonia. Its virulence was maintained by alternate passage of the culture through mice and veal infusion broth.

In the final test exactly 0.2 c.c. of a 1:1,296 dilution of a standard broth culture was injected subcutaneously over the abdomen in each animal. Following injection, the mice were observed hourly and the time

of death of each animal was recorded to determine the survival time. The heart's blood obtained post mortem was cultured for twelve to twenty-four hours in veal infusion broth for identification of the microorganism by the Neufeld typing method.

In all, thirteen series of experiments were carried out involving a total of 100 animals on each diet. The experimental data obtained were subjected to statistical analysis with the assistance of members of the Department of Biostatistics of the University of Minnesota through the courtesy of Professor Alan E. Treloar.

EXPERIMENTAL RESULTS

1. *Effects of Special Diets per se on Growth and Well-Being.*—In order to determine the effects of the experimental diets per se on growth and survival time of young mice, preliminary feeding experiments were carried out as follows: Groups of six young mice (weight, 12 Gm.) were placed on each of the diets to be used in subsequent experiments and also on more extreme diets in which the protein allowance was as low as 1 to 3 per cent of the dry weight. It was found that animals on diets containing less than 4.5 per cent of protein lost weight and did not survive six weeks. Such diets were not used, therefore, in the subsequent studies on resistance to infection.

The average weight curves for the groups of mice (50 animals in each group) maintained on the various synthetic diets finally used in the resistance experiments and also average weight curves for mice on a commercial stock diet (P. D. C.) are shown in Fig. 1.

It will be seen that the best weight records for animals on the synthetic diets were shown by the groups of mice maintained on the control diet S_1 and on the high carbohydrate, medium protein, low fat diet, S_3. The poorest records were those of animals given the low protein diets, S_2 and S_6. The proprietary stock diet (P. D. C.) proved to be clearly superior to the other diets as regards weight gain. However, the general well-being of the animals in all groups appeared to be satisfactory at the time of inoculation, as judged by general appearance (activity, hair, mucous membranes) and freedom from signs of disease. Nevertheless, the superior weight record of animals maintained on the proprietary diet suggests the possibility that the more refined diets shared some common minor defect, such as an inadequacy of vitamin C.

2. *Effects of Varying Proportions of Protein, Fat, and Carbohydrate on Resistance to Infection.*—The effects of the diets listed above on survival time of animals after inoculation with virulent pneumococci were determined in thirteen series of experiments, involving a total of 100 mice on each diet. In order to conserve space, postinoculation survival times of individual animals are omitted from Table II, which summarizes the averages for each diet in the thirteen separate experiments.

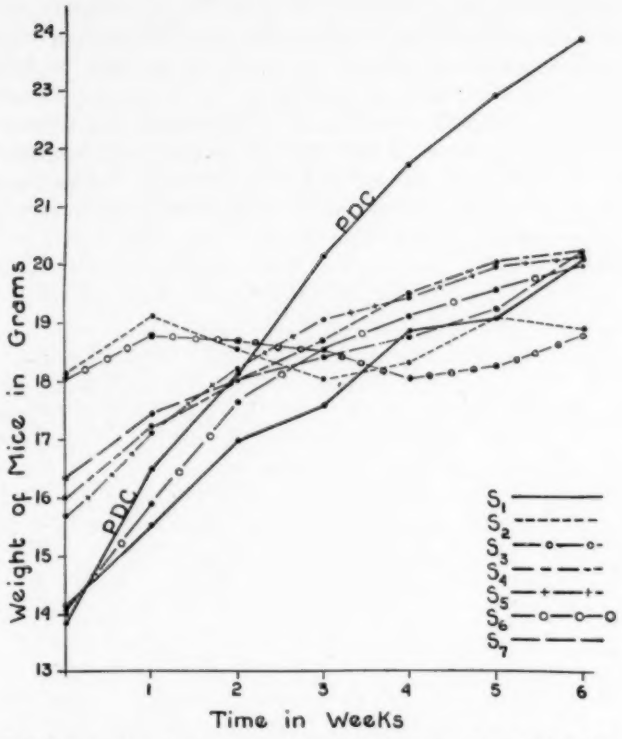

Fig. 1.—Weight curves of mice on various purified diets and on Purina dog chow.

TABLE II

AVERAGE SURVIVAL TIMES (IN HOURS) OF MICE ON VARIOUS PURIFIED DIETS AND ON PURINA DOG CHOW FOLLOWING SUBCUTANEOUS INJECTION WITH PNEUMOCOCCI (THIRTEEN EXPERIMENTS)

EXPERIMENT	NUMBER OF MICE USED	S_1	S_2	S_3	S_4	S_5	S_6	S_7	P.D.C.
1	6	34.58	22.58	36.42	46.58	43.17	22.42	31.50	32.00
2	6	33.17	20.58	37.83	44.58	45.33	22.67	32.75	35.50
3	6	31.67	21.58	41.00	43.33	44.75	22.75	33.00	33.92
4	6	33.58	21.67	34.83	42.67	46.58	20.83	31.50	33.58
5	6	35.08	19.50	38.92	45.83	45.08	23.25	30.33	33.33
6	6	35.42	21.50	38.17	39.00	43.92	21.50	32.83	32.92
7	6	38.33	20.17	37.83	43.42	44.00	20.75	34.50	32.00
8	8	36.00	21.69	38.13	47.00	44.25	21.44	52.50	32.94
9	10	35.05	20.65	38.35	42.95	53.90	21.95	32.90	34.75
10	10	35.10	22.90	35.75	41.20	43.15	21.40	31.65	35.65
11	10	33.20	21.05	34.25	42.05	43.35	21.55	31.20	36.45
12	10	35.00	22.70	36.85	43.35	41.35	21.00	30.85	34.65
13	10	35.10	21.85	33.90	43.50	45.05	21.95	32.55	35.85

DISCUSSION OF RESULTS

From these results it is quite apparent that the resistance of white mice to an experimentally induced pneumococcic infection was influenced significantly by varying the proportions of the primary food substances in the diet. The postinoculation survival time of two comparatively large series of young mice maintained for six weeks on diets containing respectively 55 and 60 per cent of protein by weight (diets S_5 and S_4) was more than double that of similar animals kept for the same period of time on diets containing either 4.5 or 10 per cent protein by weight (diets S_2 and S_6). The survival times of similar series of animals maintained for six weeks on the other diets tested (S_1, S_3, S_7, and P. D. C). were intermediate between these extremes.

The data presented afford some information likewise regarding the other two variables in the problem; namely, the fat and carbohydrate effects. That the excessively high content (76 per cent) of carbohydrate in diet S_2 does not account for the very short postinoculation survival time (twenty-one hours) of the animals maintained on it is shown by a comparison of these results with those of the experiments with diet S_3. In spite of the fact that the latter diet contained 78 per cent carbohydrate, the average survival time was 36.8 hours. Contrary to what might have been expected in the light of empirical observations already referred to, the high fat diet (S_6), containing 53 per cent fat and 10 per cent protein, was definitely inferior to the high carbohydrate diet (S_3), also containing 10 per cent protein, as regards the effect upon resistance to infection. It should be noted that the high fat diets (S_6 and S_7) contain too much carbohydrate or protein to be ketogenic. Therefore, these experiments do not exactly test the effects of the ketogenic diet on resistance to infection. Comparison of the average survival time (thirty-two hours) of the series of animals maintained on diet S_7 (20 per cent protein) with that (twenty-one hours) of the series on diet S_6 (10 per cent protein) shows again the superior value of protein as regards effect upon resistance to infection. The two diets contained the same amount of fat (53 per cent).

STATISTICAL ANALYSIS OF RESULTS

The results of the analysis of variance are summarized in Table III. Reference to the table will reveal tests for significance of variations between the various diets and between experiments, as well as interaction of these two factors. Conclusive evidence is furnished that the survival times of the animals were governed by the type of diet fed the animals. The probability of obtaining as large a value as $F = 94.08$ through errors of random sampling is infinitesimal. Variations between experiments and the interaction of experiments and diets are smaller than the known residual error to a significant degree. This result calls for an investigation of the possibility of bias. It can most reasonably be explained by

selection of animals at the start of each experiment so that they would be within a certain weight range. This purposeful selection had to be done in order to conserve time and to avoid variations which might result from weight differences. Truly random samples would then have given greater variances than those in Table III, probably removing the "between experiments" and "interaction" from the significantly low category and undoubtedly leaving the "between diets" variance as highly significant in relation to the residual error.

TABLE III

SUMMARY OF STATISTICAL DATA ON SURVIVAL TIMES OF MICE ON PURIFIED DIETS AND ON PURINA DOG CHOW, FOLLOWING SUBCUTANEOUS INJECTION WITH PNEUMOCOCCI

EXPERIMENT	MEAN	DIET	MEAN
1	33.656250	S_1	34.730
2	34.052083	S_2	21.505
3	34.000000	S_3	36.860
4	33.156250	S_4	43.390
5	33.916666	S_5	44.990
6	33.031250	S_6	21.690
7	33.875000	S_7	32.100
8	34.242188	P.D.C.	34.365
9	35.062500	Mean for Total:	33.70375
10	33.343750		
11	32.887500		
12	33.218750		
13	33.718750		

	DEGREE FREEDOM	S.S.	VARIANCE	F.
Between diets	7	52,836.694	7,548.10	94.08
Between experiments	12	298.581	24.88	3.22
Interaction	84	2,169.091	25.82	3.11
Residual	696	55,838.423	80.23	-
Total	799	111,142.789		

$n_1 = 12$; $n_2 = 700$; $F_{.05} = 1.77$; $F_{.01} = 2.21$; $F_{.001} = 2.79$.
$n_1 = 84$; $n_2 = 700$; $F_{.05} = 1.29$; $F_{.01} = 1.42$; $F_{.001} = 1.40$.
n, degree of freedom.
S. S. = n × variance.

$$F. = \frac{\text{larger mean square}}{\text{smaller mean square}}$$

COMMENT

The nature of the mechanism by which variations in the protein intake affect resistance to infection must remain obscure until further immunologic investigations have been made. It would appear from the results of the present study that prolonged use of an extremely low protein diet (e.g., 4.5 per cent) decreases resistance, whereas an intake three times as great as that ordinarily considered adequate for optimal general nutrition actually increases resistance to infection. Dietary deficiency in protein severe enough to cause hypoproteinemia with its resultant "waterlogging" of the tissues (starvation edema) might be assumed to impair immunity in a way comparable to that empirically observed in lipoid nephrosis in which the hypoproteinemic edema is due

not to a lessened intake of protein but to excessive loss of serum protein by way of the kidneys. Edema of detectable degree was not observed, however, in any of the experimental mice in the present investigation. Farr[8] has made the important observation with regard to nephrosis that a severe hypoaminoacidema occurs during the active phase of the disorder. Moreover, he has recorded data which indicate an increase in resistance to infection following intravenous administration of amino acids, both in nephrosis and in pneumonia.

It has been demonstrated by Madden and Whipple[9] that serum proteins given intravenously enter into the general protein metabolism of the body and can, therefore, replace dietary protein to a large degree. Considered in the light of this observation, the present experimental results suggest that the clinically observed therapeutic effectiveness of blood transfusion in certain acute infections may be due, in part, to nonspecific effects on the general protein metabolism. This is tentatively conceived to involve a mechanism quite different from that concerned in the acute response to foreign protein, "shock" therapy. Whether or not oxblood fibrin, the particular protein selected for use in the present studies, is unique in respect to its influence on resistance to infection cannot be said with certainty until further tests have been made. At the present time, however, there would appear to be no reason for assuming that it is superior to other food proteins capable of furnishing the same amino acids.

SUMMARY

The effects of extreme variations in the proportions of protein, fat, and carbohydrate in the diet on resistance to infection were investigated. The experimental procedure employed was to feed groups of young mice for six weeks on special diets and then to inoculate them with a standard, multiple-lethal dose of virulent pneumococci. The postinoculation survival time was regarded as a measure of resistance to infection. The test diets were constructed so as to represent all combinations of protein, fat, and carbohydrate at high, medium, and low levels. In all, thirteen experiments were carried out, involving a total of 100 animals on each of the eight diets tested.

Statistically significant differences in the postinoculation survival time of animals maintained on diets, varying widely in their protein, fat, and carbohydrate content, indicate that resistance to infection is affected by these primary food substances. The most significant result was that pertaining to the effect of protein. Animals which had been maintained on a very low protein intake showed a greatly decreased postinoculation survival time, as compared with control animals. On the other hand, those which had been subjected to an excessively high protein intake showed a distinct lengthening of the survival time after inoculation.

Contrary to what had been expected, high carbohydrate feeding per se failed to reduce resistance if the protein content of the diet was 10 per cent or above.

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CALSOY

A Soybean Substitute for Milk

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THE more widespread recognition that various milks may be agents in the production of allergic manifestations has created a greater demand for milk substitutes in the dietary management of infants and children. Numerous preparations have appeared in the literature, chief of which are those derived from soybeans. The rather high cost of the soybean milk substitutes available on the market makes them almost prohibitive not only for outpatient use, but also in many instances for patients in private practice. From the effort to secure an inexpensive milk substitute, the following soybean recipe, which for convenience was named calsoy, was developed in the Allergy Clinic and dietetic laboratories of the Los Angeles Children's Hospital.

RECIPE

Ingredients Necessary.—

1. 160 Gm. of soybean flour or 1⅓ standard kitchen cupfuls
2. 4 Gm. of clear gelatin or 1 standard kitchen teaspoonful
3. 840 c.c. water or 3½ standard kitchen cupfuls
4. 1 Gm. of calcium gluconate or 1 level standard kitchen teaspoonful
5. 1 teaspoonful salt

Method of Preparation.—

1. Soak the gelatin in 120 c.c. of cold water (½ standard kitchen cupful) for five minutes. Then heat the mixture until the gelatin is completely dissolved.
2. Add the gelatin mixture to the remaining 720 c.c. of water.
3. Mix the soybean flour and the calcium gluconate.
4. Slowly sprinkle the flour and calcium mixture into the gelatin mixture, beating constantly with a dover beater or an electric mixer. It is important that the flour be sprinkled into the water to avoid a gummy mass.
5. Heat the mixture over a direct flame until it comes to a boil, beating constantly to keep smooth.
6. Transfer to a boiling double boiler and cook two hours, keeping the cover on tightly. Beat the mixture with a beater one-half a minute every ten to fifteen minutes.

From the Allergy Service of Dr. George Piness, Children's Hospital, Los Angeles.

7. To the resulting mixture add enough hot water to restore the volume to 1,000 Gm. (1 quart). Cool and store in a cold place. This can be stored one week.

8. Heat when serving. Sugar modifiers or fruit concentrates may be added if desired.

COMMENT

By comparing the figures of Table I it will be noted that calsoy has an available calcium content which is practically equal to that of cow's milk and that the calcium-phosphorus ratio of calsoy is the same that normally occurs in cow's milk.

TABLE I

		CARB. (GM.)	PRO. (GM.)	FAT (GM.)	CALORIES	CALCIUM (GM.)	PHOSPHORUS (GM.)
Cow's milk*	960 c.c.	48	29	38	650	1.38	0.835
Calsoy†	960 c.c.	19	64	32	620	1.30	0.896

*Bodansky, *Introduction to Biological Chemistry*, ed. 4, New York, 1938, John Wiley & Sons, Inc.

†Unpublished Data of the Bureau of Home Economics.

Because only 22 per cent of the carbohydrate of soybean is available to the body, the carbohydrate percentage is extremely low. When necessary, the carbohydrate content can be increased readily to any desired percentage by the addition of carbohydrate modifiers. In our experience, no great addition of carbohydrate has been found necessary, as the caloric value of the suggested recipe is almost equivalent to that of whole cow's milk.

The protein content of the mixture is a little more than double that of cow's milk. This may be looked upon as a desirable feature. Soybean products are frequently not well tolerated; especially by very young infants. The low carbohydrate percentage decreases the likelihood of carbohydrate fermentation, while the high protein content, we feel, decreases peristaltic activity.

By using the high fat soybean flour available on the market, calsoy presents a fat concentration comparable to that found in cow's milk.

A bacteriologic study of the product has demonstrated that the mixture can be kept in the refrigerator for a week without spoiling. This would permit making a week's supply of the mixture at one time.

3875 WILSHIRE BOULEVARD

SARCOIDOSIS

Case Report

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IT HAS been mentioned in a recent editorial[1] that "medical literature reveals a renewed interest in this disease." Pediatric journals, however, record very few instances of this entity and for this reason this case report is submitted for publication.

Sarcoid is defined at present as a somewhat rare group of inflammatory tumors composed of nodules of epithelioid cells. The names used to designate different clinical varieties of this entity depend upon the localization in various tissues and organs. Thus we have among those more commonly known the lupus pernio of Besnier,[2] the subcutaneous sarcoid of Darier-Roussy,[3] the multiple benign sarcoid of Boeck,[4] which he later subdivided into three varieties, and finally the benign lymphogranulomatosis of Schaumann.[5] The use of the term sarcoidosis is not meant to introduce an additional name but only to indicate a generalized distribution and, no doubt, is synonymous with the latter. Osteitis tuberculosa multiplex cystica of Jüngling[6] by some and uveoparotid fever by others[7] are considered to be varieties of sarcoidosis.

Sarcoidosis has been described as occurring in children,[7] usually in the older age groups.[5, 8] Roos[9] and Naumann[10] have described this condition in younger children.

The case being presented in no way contributes to the final settlement of the controversy as to the etiology and nature of this disease. It does, however, present features which are unusual and not generally observed in cases of sarcoidosis.

CASE HISTORY

The first admission of a 25-month-old female child with chief complaints of not eating well and a weight loss was on May 24, 1939.

Her health had been comparatively good up to the age of 9 months when she began having frequent colds and sore throats associated with mildly inflamed ears. The infant continued to eat well and gain weight up to the age of 12 months when the weight was 23 pounds. At this time she began to eat poorly and at 18 months the weight was 20 pounds.

In November, 1938, the child had pertussis. This was followed in January of 1939 with two colds both of which were associated with inflamed ears that did not drain.

Two weeks before admission and adenoidectomy was done at another institution; the weight had gone down an additional pound to 19 pounds. The mother stated that "the child would drink only milk and other liquids, also vegetables but no other foodstuffs."

From the Departments of Pediatrics and Pathology, New York Postgraduate Medical School and Hospital, New York, N. Y.

The only medication was ½ an ounce of cod-liver oil daily. Mild constipation was present requiring enemas every other day. There was no fever, vomiting, or any other symptomatology. Birth and developmental history were normal. There was a negative history of familial diseases. This had been the only pregnancy.

The outstanding physical finding was the general appearance presented. Despite the Irish-American parentage, the child, whose hair and skin were fair, could more easily have been taken to be of Mediterranean parentage with more than a suggestion of a mongoloid appearance. The skin was very pale and lemon yellow. Nutrition was very poor and the child was weak. The ears, nose, and throat were negative except for slight nasal discharge. Dentition was fair. The inguinal and cervical nodes were very slightly enlarged, discrete, and nontender. There was diminished expansion over the left side with dulness anteriorly and posteriorly over the lower lobe but no change in breath sounds and no râles. The heart was negative; the liver and spleen were not palpable. Abdominal and rectal examinations revealed no masses; examination of the extremities proved to be negative.

The impression on admission was a primary blood dyscrasia, type to be determined.

CLINICAL COURSE

The admission weight was 19 pounds and the temperature was 100.6° F.; pulse, 140; and respirations, 28. The child was put on a high-vitamin, high-caloric diet, but despite our use of methods, which varied from the extreme of judicious neglect to the opposite one of gavage with a regime of insulin therapy interspersed between the two, the antipathy to any food other than liquids was not overcome. The weight curve with only minor fluctuations presented a downward trend to a level around 17 pounds.

The Wassermann was negative and also throughout the course the urine remained negative to chemical and microscopic examinations. The Mantoux 1-1,000 was negative. Our greatest interest was in the blood counts which were as reported in Table I.

X-rays of the long bones and skull were reported as showing proliferative periosteal reactive changes with numerous small-sized areas of rarefaction in the cortices both in the compact and cancellous portions with natural break in the outer cortex in small areas. Multiple small areas of porosity were discernible throughout the bones of the vault but with no reactive periosteal changes demonstrable here. The picture was suggestive of a severe blood dyscrasia (probably leucemic). X-ray of the chest revealed a slight degree of lymphoid nodulation at the hilus with further slight reticulation and mottling in the central lung fields, perhaps of a lymphocytic character. The areas of rarefaction in the cancellous portions and the cortices of the osseous structures suggested a probable leucemia.

Differential smear of material obtained by sternal puncture to one observer showed the cell types ordinarily seen in bone marrow with no predominance of any one type, the impression being that a diagnosis was not warranted from these smears. The other observer found a predominance of lymphocytes, 57 per cent of the total. It was the impression of this observer that the lymphocytes in the marrow differential suggested lymphatic leucemia.

Although the clinical picture and work up to date were somewhat in favor of this diagnosis, there were some features which, to say the least, were atypical; viz., the peripheral blood picture, the absence of splenic and hepatic enlargement, and the minimal amount of lymphadenopathy. The clinicians in attendance were divided in their opinions, but the majority did favor the diagnosis of lymphatic leucemia. The only other diagnosis offered was Hand-Christian-Schüller disease. This did not, however, alter our therapy, which consisted of supportive measures. Chiefly, these were repeated transfusions, hematinics, and diet with the poor results previously recorded and also as reflected in the blood counts.

Throughout the whole hospital course and starting the fifth day after admission, there were irregular and almost daily elevated fluctuations of temperature to 102 to 103° and frequently to 104°.

There was no change observed in the physical findings except for slowly progressive lymphadenopathy. The spleen had been palpated at the costal margin on one occasion. Repeated blood counts were negative.

Biopsy of an inguinal lymph node, which at the time of operation was thought to be a leucemic node, on microscopic examination revealed only a slight chronic lymphadenitis.

TABLE I

DATE	R.B.C.	W.B.C.	PLATELET	HGB.	TRANS.*	POLY.	EO.	LYM.	MO.	RET. (%)	B.T.	C.T.
5/25	1,790,000	5,400	105,000	4.0	175	36		64			8	4-8
6/ 2	3,100,000	5,800		7.3	175	47		52	1			
6/ 7	3,310,000	6,450		10.9		46		54				
6/ 8	3,850,000	9,000		12.0		47		48	5			
6/ 9	3,310,000	9,000		16.2		42		58				
6/12	3,350,000	8,875		10.7		38†		59	2			
6/14	3,250,000	10,000		9.2		41		58	1			
6/16	3,010,000	6,050		9.1		38		61	1			
6/19	2,800,000	9,950		9.0		41		59				
6/23	2,600,000	10,000	70,000	7.6		44	3	52	1	2.2		
6/26	2,140,000	6,050		6.8	175	37	1	62				
6/30	2,640,000	5,750		8.3		33		66	1			
7/ 3	2,880,000	6,850		8.1		37		62	1			
7/ 7	2,210,000	5,900		7.2		28	1	70	1			
7/10	2,050,000	5,800		6.3	175	30	1	63				
7/17	2,260,000	5,150		7.3		21		79				
7/19	1,620,000	6,650	30,000	5.1		18		78	4	1	3	6
7/24	1,560,000	5,450	130,000	4.6	200	19‡		80		1		
7/31	1,840,000	4,500	126,000	6.6		11		88	1		2½	4½
8/ 4	1,280,000	12,350		4.3	200	24		76				
8/ 7	1,620,000	4,700	62,000	4.6	120	28		72			3	4
8/14	800,000	4,150	62,000	2.6		31		69				

*Cubic centimeters of blood given after blood count on date recorded.
†Metamyelocyte.
‡Myelocyte.

Blood Chemistry

N.P.N.	24.0
Urea	9.0
Glucose	70
Chol.	165
Chol. Esters	40
Icterus Index	3.1
Calcium	10.8
Phosphorus	4.1

Phosphatase Activity
3.9 units per hour
R.B.C. fragility 0.54-0.315%

Sternal Puncture

Nucleated cells	77,750
Polys	31%
Metamyelocytes	3%
Myelocytes	5%
Myeloblasts	3%
Monocytes	1%
Lymphocytes	57%
Erythronormoblasts	15%

On July 25, in addition to the cervical, axillary, and inguinal lymphadenopathy, the occipital nodes became palpable and continued to increase in size rather rapidly. In addition, purpuric spots appeared over the anterior abdominal wall.

On August 3 it was noted that extreme thirst was present and also that the child was voiding frequently in fairly large amounts. Measurement of the intake and output showed both to be about 2,000 c.c. per twenty-four hours. After limiting

the fluids to 1,000 c.c. for a day, the specific gravity was 1.001; limiting the fluids to 750 c.c. the next day resulted in a specific gravity of 1.006.

On August 4 biopsy of a suboccipital node was done and was reported as showing chronic granulomatous inflammation, suggesting tuberculosis. A 1-500 Mantoux done at this time was negative.

The spleen and liver became palpable 1 to 2 cm. below the costal margin. The child's condition continued to get worse, and she expired on Aug. 15, 1939.

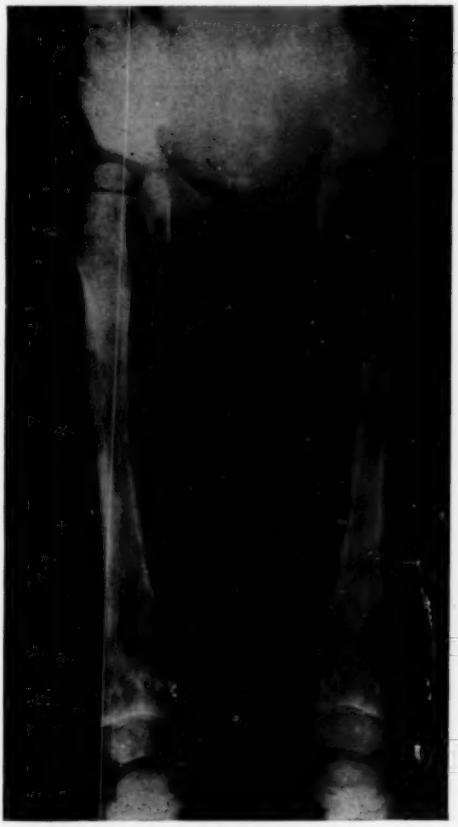

Fig. 1.—Proliferative periosteal reaction seen along shafts of femurs.

GROSS ANATOMY

Thoracic Cavity.—There is no deformity of the bony thorax. The lungs lie free within their pleural cavities. There is no increase in pleural fluid.

Pericardial Sac.—The mediastinal fat covering the pericardium is less than normal in amount. The heart lies free within its pericardial sac, which contains about 50 c.c. of clear straw-colored fluid.

Peritoneal Cavity.—The peritoneum is smooth and glistening throughout. There are no distended loops of bowel and no increase in peritoneal fluid. The diaphragm is at the level of the third intercostal space on the right and the fourth space on the left side.

Heart.—The heart weighs 75 Gm. There is a decreased amount of epicardial fat. On section the myocardium throughout has a "boiled" grayish-red color. The endocardium of the right auricle is normal. The leaflets of the tricuspid valve are thin and smooth. The right ventricular endocardium is normal. There is no flattening of the papillary muscles. The pulmonic valve leaflets are thin and smooth.

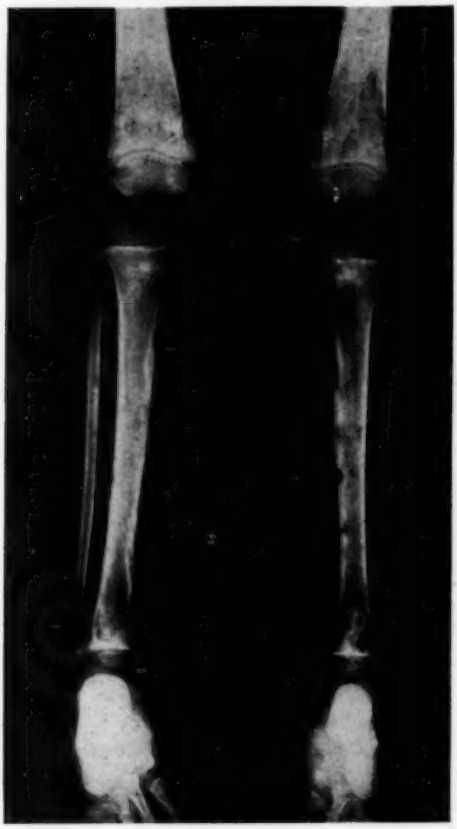

Fig. 2.—Proliferative periosteal reaction less marked than in Fig. 1, but the circumscribed areas of rarefaction are well seen.

The left auricular endocardium is smooth and glistening throughout. The leaflets of the mitral valve are thin and smooth and their chordae tendineae are normal. The endocardium of the left ventricle is normal. The leaflets of the aortic valve are normal.

Aorta.—The aorta is elastic. Its intima is smooth and glistening.

Lungs.—The trachea and bronchi are normal. The right lung weighs 135 Gm. The pleura is smooth and glistening. On section there are many pin-point, yellowish-gray nodules throughout the pulmonary substance. There are no areas of consolidation. On pressure, thin frothy fluid escapes from the alveoli.

The left lung weighs 100 Gm. It is similar to the right.

Liver.—The liver extends 2 cm. below the right costal margin in the midclavicular line and 3 cm. below the xiphoid process. It weighs 400 Gm. Its edges are sharp. On section, the architectural markings are distorted by congestion. The gall bladder and extrahepatic ducts are normal.

Spleen.—The spleen is grayish red. It measures 9 × 6 × 4 cm. and weighs 80 Gm. On section the pulp is fibrous and the follicle markings are exaggerated.

Pancreas.—The pancreas is brownish yellow, firm, and lobulated. It is normal in size, shape, and position.

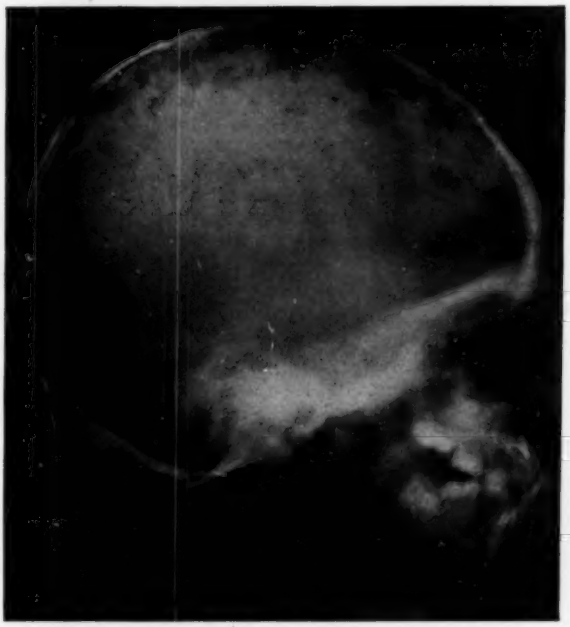

Fig. 3.—"Punched-out" areas of porosity with no reactive periosteal changes.

Adrenals.—The adrenals are normal in size, shape, and position. On section, there is a normal amount of yellow cortical lipoid.

Kidneys.—Together the kidneys weigh 110 Gm. The surfaces are smooth and yellow and the capsules strip easily. On section, there is a normal amount of cortex and medulla. The cut surface is glistening, waxy, and yellow. The calyces, pelves, ureters, and bladder are normal.

Gastrointestinal Tract.—The mucosa of the esophagus is normal. The stomach is empty and its rugae flattened. The small intestine contains a small amount of chyme. Its mucosa and serosa are normal.

The large intestine is filled with small scybalous masses. Its serosa and mucosa are normal.

Thyroid.—The thyroid is normal in size, shape, and position. On section, there is uniform diffuse distribution of small pin-point areas of colloid.

Lymph Nodes.—There are firm, discrete, homogeneous nodes 5 to 10 mm. in diameter in both cervical areas, about the tracheal bifurcation, and within the folds of the mesentery. They are homogeneously gray on section.

Bone Marrow.—A portion of sternal bone marrow is alternately red and yellow in areas.

Brain.—Apart from congestion of the pial vessels, there are insignificant gross alterations.

GROSS ANATOMICAL DIAGNOSIS

Miliary tuberculosis of lungs; edema of lungs; parenchymatous degeneration of heart and kidneys; passive congestion of liver, spleen, and kidneys; generalized enlargement of lymph nodes (cervical, tracheobronchial, mesenteric, inguinal).

MICROSCOPIC ANATOMY

Heart.—There is little pericardial fat, but there is increase of poorly cellular collagenous connective tissue, most dense around the coronary artery. The vessels are generally unaltered and those in the myocardium are congested.

Lungs.—The bronchial and bronchiolar epithelium is poorly preserved but is not diseased. In the submucosa there are lymphocytes and plasma cells, densest in the bronchioles whence the infiltration extends into adjacent alveolar walls and, in some places, into alveolar spaces. Interlobular septa are widened by edema. Most of the alveoli contain varying numbers of red cells and desquamated alveolar lining cells, many of the latter with ingested blood pigment. Edema fluid is also present in many alveoli.

The most striking feature is the presence of granulomas intimately related to the blood vessels, especially arterioles. The granulomas are not only adventitial, but also are subendothelial. The adventitial granulomas replace adjacent alveoli. The granulomas are formed of epithelioid cells which in some are concentrically arranged. Lymphocytic infiltration is seen, generally peripherally. Giant cells are present in small numbers and are not of the Langhans' type. A few of the granulomas are partly fibrotic, apparently of older occurrence. In a section appropriately stained, no acid-fast bacilli are recognized.

In several places in bronchial walls, there are collections of multinucleated giant cells surrounding fibers which are doubly refractile and which have a central pigmented area, suggesting hair. One such foreign body granuloma is present at the junction of several alveoli.

Liver.—There is central congestion in the lobules, the sinusoids of which contain relatively large numbers of leucocytes. The liver cords are finely vacuolated in the areas of maximum congestion. There are several small focal collections of epithelioid cells without associated necrosis or giant cells.

Spleen.—The trabeculae are unchanged. The follicles are reduced in number and in some of them the arterioles have hyalinized walls. The red pulp is the seat of an intensive and extensive granulomatous process. In many places there are distinct granulomas, while in most areas there are columns of granulation tissue. The granulation tissue, especially in the granulomas, compresses and destroys the follicles.

The granulation tissue is formed of epithelioid cells which, in the follicles, are concentrically arranged. Many of the epithelioid cells contain brown pigment, probably hematogenous. The numerous giant cells throughout the granulation tissue are also phagocytic. Some have brown blood pigment while others are laden with leucocytes. Here, as in the lung, the giant cells are of the foreign body type; true Langhans' cells are virtually absent. The splenic tissue, intervening between the foci of granulation tissue, is overrun by lymphocytes and plasma cells. Acid-fast bacilli are not seen. Blood formation is noted.

Pancreas.—Except for post-mortem changes, the pancreatic structures are relatively unchanged.

Adrenal.—In the adrenal cortex, the zona glomerulosa and the outer portion of the zona fasciculata are formed of vacuolated or storage cells; the remainder of the cortex is composed of cells with solid cytoplasm, so-called chief or principal cells.

In the cortex there are several "adenomas," the cells of which are generally less vacuolated than those of the adjacent cortex.

Kidney.—In general, the kidney is well preserved. In the walls of the pelvic vessels are granulomas similar to those described in the lung. There is also localized granulation tissue in the same area.

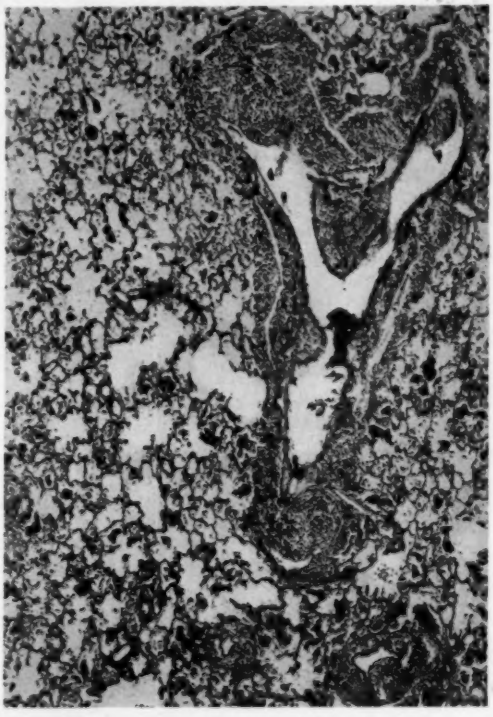

Fig. 4.—Section of lung (×75), demonstrating adventitial and subendothelial involvement of blood vessels by granulomas.

Glomeruli and tubules are generally unaltered. There is, however, a radially linear zone in the cortex in which glomeruli are in varying stages of fibrotic obliteration. Here, there are tubules which are greatly dilated. Their epithelium is flattened and they contain coagulated albumin. There is distinct scarring of the stroma near the cortical surface associated with atrophy of the tubules in it.

Thyroid.—The acini are generally similar but several lobules have dilated acini. In the small acini there is marked vacuolation and reticulation of the eosinophilic colloid in the dilated alveoli. There is only slight peripheral vacuolation.

Lymph Nodes.—In the nodes there are many surviving follicles in the granulomatous process which has attacked the node in diffuse fashion, as seen in lesser degree in the spleen. In the peripheral sinuses there are innumerable giant cells, while centrally the giant cells are less prominent because of the many monocytes and reticulum cells.

Another section is generally similar, except that here many of the giant cells are even larger than in the previous section. Few are of the Langhans' type; phagocytized leucocytes are seen in some of them, as well as brown pigment, probably hemotogenous.

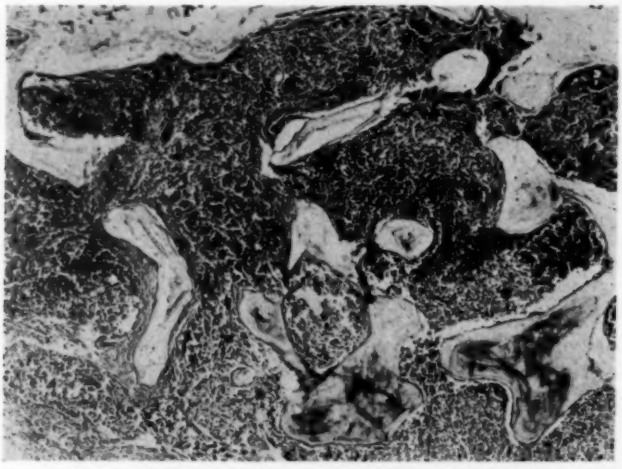

Fig. 5.—Section of sternum (×75). The granulomatous involvement almost completely replaces the marrow.

Fig. 6.—Section of skull (×65), showing presence of granulomas within diploe to give peculiar x-ray findings; bone formation is prominent.

Bone.—In section of the sternum there is almost complete replacement of the marrow in many places by granulation tissue. Here, however, there is much fibroblastic connective tissue. Giant cells are prominent. In the surviving myeloid tissue there are small numbers of myeloid cells but chiefly red cells and their forerunners.

There are also megakaryocytes. Most of the bony trabeculae have the major portions of their surfaces covered by osteoblasts, but there are surfaces on which Howslip's lacunae are seen, both with and without osteoclasts.

In the skull the tables are porotic. The most marked activity is in the diploe. Bone formation is prominent with the bony surfaces covered by osteoblasts. Bone formation is also connective tissue. The marrow is of fibrous character with foci of giant cells, suggesting osteoclasts, surrounding round to oval spaces. The latter probably held bone fragments which fell out during preparation. There are also granulomas similar to those described in the other tissues.

Brain.—The section of the pons shows no obvious alteration. The aqueduct of sylvius is normally formed and lined.

The capsule of the pituitary body is involved in the granulomatous inflammatory process which invades the pituitary proper.

SUMMARY

This is the case of a 2-year-old child who had frequent colds and sore throats. There had been loss of weight, low-grade fever, and generalized lymphadenopathy. The blood picture was that of an anemia with low normal white count and relative lymphocytosis. X-rays of the bones suggested a leucemic process. The occurrence of diabetes insipidus suggested xanthomatosis. Biopsy of bone marrow on two occasions did not yield information of importance, but a lymph node showed lesions suggesting tuberculosis.

At autopsy there were miliary lesions in several organs that strongly suggested tuberculosis. These lesions had "epithelioid" cells, but there was no necrosis and in some organs no giant cells. The latter were particularly numerous in the lymph nodes where the lesions were more diffuse. In the spleen the tubercles contained an unusual amount of hemosiderin, and although there were only a few miliary nodules, there was extensive fibrosis. The bone marrow, similarly, had only a few miliary nodules but there was extensive fibrosis present.

The case may be one of miliary tuberculosis but the absence of necrosis suggests that it is of the type usually described as Boeck's sarcoid. The differentiation of these two conditions has always been a matter of discussion and it is not yet settled whether sarcoid is, indeed, a form of tuberculosis. This patient is much younger than in the usual cases of sarcoid.

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EPIDERMOID CARCINOMA IN THE FIRST DECADE OF LIFE

Report of a Case

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CERTAIN groups of tumors are distinctive for various periods of life. Carcinoma occurs most frequently in later adult life, sarcoma in youth and early middle age, and embryonic new growths in the first decade of life. Specific childhood tumors include, in the main, teratomas, embryomas, and tumors arising from the developing nervous system, such as gliomas and sympathicoblastomas. Ewing[1] has indicated the uniqueness of tumors of early life in the statement "tumors of childhood should include only those characteristic of the first ten years of life."

The incidence of carcinoma in childhood is difficult to estimate due to the fact that statistical tabulations of all forms of malignant neoplasms are included under the designation "cancer" and are not classified according to cell type.

Helmholz[2] in 1931 reported 714 cases of cancer in persons under 15 years of age. Of this number, 97 per cent were sarcomas. Three per cent included three carcinomas of the skin, and all three were found in persons over 11 years of age. Pearl and Bacon[3] reviewed 6,670 autopsies at Johns Hopkins Hospital and found fifty-nine malignant tumors occurring in persons under the age of 20 years. There were no carcinomas in this group. A detailed statistical report,[4] with 16,565 malignant tumors observed at all ages, came from the Memorial Hospital in New York in 1930. Among this number, there were fourteen carcinomas in individuals up to and including 10 years of age. It is interesting that about half of these carcinomas originated in the Schneiderian membrane or in relation to lymphoid tissue in the region of the pharynx. Only two of the total fourteen were epidermoid in type. One of these epidermoid tumors was found on the perineal skin of an infant 15 months of age; the second arose in the buccal mucosa of a child of 14 years. In 1939 a second report[5] of 4,500 tumors of head and neck gave an incidence of 1 per cent of carcinomas occurring at this site in persons under the age of 15 years. Martin,[6] analyzing this second report, found two carcinomas of the lip and three on the skin of the face. The youngest patient was 20 months old. A squamous-cell carcinoma of the tongue in a newborn infant was described by Frank, Enfield, and Miller[7] in 1936.

Since carcinoma in children under 10 years of age is rare, it may be of interest to place this case on record. The carcinoma described herein

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originated in the inner surface of the cheek of an infant 4 months of age. It was surrounded by mucoid material which had apparently escaped from an injured buccal gland in the vicinity. It seems possible that the mucus may have been a potent factor in the pathogenesis of the tumor.

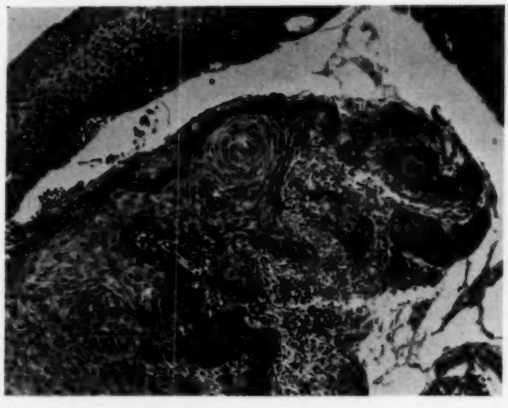

Fig. 1.—Epidermoid carcinoma infiltrating subcutaneous tissue of cheek. Hematoxylin and eosin stain. ×120.

Fig. 2.—Infiltration of mucus in the vicinity of tumor growth and exudate with compound granular cells. Hematoxylin and eosin stain. ×120.

The patient, J. E., a 4-month-old white infant was admitted to Children's Hospital on Feb. 18, 1941, on the service of Dr. Elmer A. S. King for treatment of a growth on the inside of the right cheek. The growth was located about three-fourths of an inch from the corner of the mouth. The mother first noticed a swelling in this area four weeks previous to admission. The family physician incised the swelling a week after it was discovered and obtained a thick, bloodstained, nonpurulent fluid. The incision healed normally, but the mass gradually increased in size until the time of admission.

The mother's history revealed that pregnancy had been normal. The infant weighed 10 pounds, 3 ounces at birth, and the general health of the child has been

excellent. Further family history revealed that one sibling, 3 years old, was living and well. One had died at the age of 2 years as a result of an operation for "cyst of the pancreas."

Physical examination at the time of admission showed a well-developed, well-nourished 4-month-old infant. Head, eyes, ears, and nose were essentially negative. On the right anterior buccal mucosa, near the angle of the mouth, was a polypoid growth approximately 0.5 cm. in diameter. It was pink, soft, and not tender. There was no cervical or general lymphadenopathy. Chest and abdomen revealed no abnormalities. Impression on admission was lymphangioma of mouth.

The day following admission the growth was removed under ether anesthesia. Convalescence was uneventful, and the patient was discharged on Feb. 23, 1941. The scar appeared normal when examined ten months after operation.

Routine laboratory data including complete blood count, urinalysis, and throat culture were essentially normal.

Gross Examination.—The gross specimen measured approximately 0.5 × 0.4 × 0.3 cm. The tissue was firm and pink in color.

Microscopic Examination.—Serial microscopic sections showed that the tumor mass occupied an area approximately 1 mm. in diameter, situated between two down dippings of hypertrophied squamous epithelium. In the central part of the section where the tumor originated was a thinning of the overlying epithelium to about three or four layers of cells in contrast to the hypertrophied epithelium on either side. The tumor was arranged in whorls with definite pearl formation and was infiltrating the contiguous tissue. Intercellular bridges were prominent, and there was a moderate number of mitotic figures. Lobules of a buccal gland of the mixed type were seen in the underlying dermis, the ducts of which were lined by pseudostratified epithelium. The gland was surrounded by striated muscle. In the tissue surrounding the lobules was an infiltration of mucoid material which was being actively phagocyted by monocytes. Many of these had the appearance of compound granular cells, especially in one area. A nest of these cells embedded in mucoid substance which was surrounded by early organization tissue suggested that the mucoid material had escaped into the tissue some time previously. A few plasma cells, lymphocytes, and polymorphonuclears were also present.

This tumor is unique for two reasons: First, its occurrence at such an early age, and, second, its association with free mucus. The irritation of infiltrating mucus is suggested as a possible etiologic factor in the pathogenesis of the tumor.

SUMMARY

The case reported is the youngest patient with epidermoid carcinoma found in the literature. The escape of mucus in the vicinity of the developing tumor is suggested as a possible etiologic factor in the pathogenesis.

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INFLUENZAL MENINGITIS

Report of a Case With Recovery

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INFLUENZAL meningitis, caused by the *Hemophilus influenzae*, has gained considerable interest lately due to the newer methods of therapy.

Its relative frequency as the causative organism of meningitis ranks from first to fourth according to the series selected and the age groups included.[1-4] Males are more likely to be affected than females, and its incidence is highest during seasons of respiratory infections.

As there is no definite clinical pattern, delayed signs and symptoms make the diagnosis difficult. The most important signs and symptoms are vomiting, stiff neck, and increased or absent reflexes.[4] Huntington and Wilkes-Weiss[5] report that of forty-two patients, ten developed signs of meningitis after admission to the hospital, and that over one-half of the patients had otitis media or pneumonia upon admission to the hospital.

There are numerous reports in the literature regarding the therapy of influenzal meningitis. Wollstein[6] (1911) prepared anti-influenzal serum by immunizing goats. Later, other investigators developed an anti-influenzal horse serum, and then a specific rabbit serum was prepared and used by Alexander.[7-9]

Since 1936 numerous articles have appeared in the literature reporting recoveries following the use of the sulfonamides and serum (especially sulfapyridine, alone or in conjunction with serum.) With these methods of treatment, there has been a reduction in the mortality rate of this disease.

Although sulfadiazine (2-sulfanilamidopyrimidine), is one of the newer sulfonamides, numerous reports have already been published regarding its efficiency in acute infections.[10, 12, 17, 20] Sulfadiazine was first synthesized by Roblin and his co-workers.[11] It is reported that high concentrations can be obtained in the blood,[17, 18] and spinal fluid,[13-15] yet the toxic effects are few, both in the experimental animal[16] and man.[12]

It is, therefore, the purpose of this communication to present another successful combination used in one case at the Louisville City Hospital; viz., anti-influenzal rabbit serum, type "b," in conjunction with sulfadiazine.

A 2-year-old white male child was admitted to a private hospital in Louisville, Ky., July 16, 1941. The onset of his illness began the day prior to admission when the child had a high fever and started vomiting.

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On the day of admission to the hospital, it was found that he had a stiff jaw, and on the afternoon of his admission he had a generalized convulsion.

On admission, the physical examination revealed a temperature of 101° F. The child was very restless and irritable, and the only positive physical finding was a slight stiffness of his neck.

A lumbar puncture revealed turbid spinal fluid, increased pressure, a total cell count of 9,800 per cubic millimeter with 98 per cent polymorphonuclear leucocytes and 2 per cent lymphocytes, and globulin of four plus. Repeated lumbar punctures revealed 1,558 and 1,400 cells per cubic millimeter, a turbid spinal fluid, and a consistent four plus globulin. A culture of the spinal fluid showed *H. influenzae*, type "b." On admission to the hospital the white blood cell count was 7,500 per cubic millimeter with 70 per cent polymorphonuclear leucocytes and a red blood cell count of 4,360,000 per cubic millimeter and with hemoglobin of 70 per cent. During his hospitalization at the private hospital, the patient was treated with oral sulfanilamide and sulfapyridine.

His temperature ranged from 100° F. to 107° F. On July 22 he was transferred to the Children's Free Hospital of Louisville, Ky.

A lumbar puncture was repeated on admission to Children's Free Hospital. It showed a cloudy spinal fluid, a cell count of 380 per cubic millimeter, with 75 per cent polymorphonuclear leucocytes and 25 per cent lymphocytes, and globulin of one plus. The spinal fluid culture was again positive for *H. influenzae*, type "b." A lumbar puncture was repeated July 23 and showed a cell count of 1,638 per cubic millimeter with 88 per cent polymorphonuclear leucocytes and 12 per cent lymphocytes. The blood count on July 24 was 2,600,000 red blood cells per cubic millimeter with hemoglobin of 9.5 Gm. per 100 c.c. and a white blood cell count of 28,600 per cubic millimeter with 72 per cent polymorphonuclear leucocytes and 28 per cent lymphocytes. Examination of the urine showed a trace of acetone but was otherwise negative. Treatment consisted of oral sulfapyridine, transfusions, and other supporting therapy.

While the patient was at Children's Free Hospital, his temperature varied from 101° F. to 105.8° F. with no improvement of his condition. The patient was transferred to the isolation ward of the Louisville City Hospital on July 26 for serotherapy.

On admission to the isolation ward, the temperature was 102.8° F. with pulse of 160 and respirations of 74. The patient appeared acutely ill and very anemic. Examination of the eyes revealed equal, regular pupils that reacted to light. The neck stiffness was three plus. All the deep and superficial reflexes were absent except the cremasteric reflex. The Kernig and Brudzinski (contralateral) signs were positive. A lumbar puncture revealed a spinal fluid cell count of 362 per cubic millimeter with 75 per cent polymorphonuclear leucocytes and 25 per cent lymphocytes, and globulin, negative. The spinal fluid culture was again positive for *H. influenzae*. Blood culture, tuberculin, Schick, and Kahn tests were all negative.

On July 26 he was given, after a negative skin test, 25 mg.* of anti-influenzal serum, type "b," intrathecally and 25 mg. intravenously. One gram of sulfadiazine was given orally, immediately, and ½ Gm. was given every four hours. On July 30, after some improvement and again after a negative skin test, an additional 25 mg. of anti-influenzal serum, type "b" was given intrathecally and 50 mg. intravenously. All the subsequent spinal fluid cultures were negative. The cell count of the spinal fluid gradually decreased and on September 5, the total cell count was 14 cells with polymorphonuclears 3 and lymphocytes 11. The sulfadiazine concentrations in the spinal fluid ranged from 1.15 to 10.26 mg. per cent. Numerous blood transfusions were given and other supporting therapy.

*Precipitable antibody nitrogen.

The patient became rational on August 2 and the spinal fluid became permanently clear on August 5. He became afebrile on August 15. Gradually he found it possible to sit alone and to walk.

The last blood count taken before his discharge from the isolation ward of the Louisville City Hospital was 4,550,000 red blood cells per cubic millimeter with hemoglobin of 12 Gm. per 100 c.c. and a white blood cell count of 9,400 per cubic millimeter. Sulfadiazine was discontinued on September 9. Although he was given a total of 135.5 Gm. of sulfadiazine over a period of forty-five days (½ Gm. every four hours), there were no toxic effects. He was discharged from the hospital on September 15.

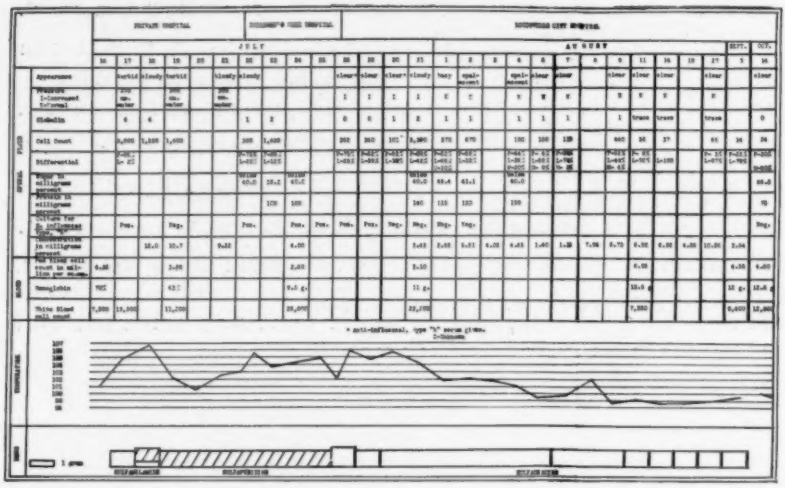

Fig. 1.

The patient was readmitted on October 14 with complaints of pain in back of his head and vomiting. The physical examination was negative with the exception of a temperature of 100.4° F. In view of the possibility of a recurrence of influenzal meningitis, a lumbar puncture was repeated which revealed a clear spinal fluid and a cell count of 24, with polymorphonuclear leucocytes 20 per cent and monocytes 80 per cent. The spinal fluid culture and globulin were both negative. After an uneventful hospitalization, he was discharged on October 16.

He has been followed in the clinic and to date has had no symptoms of recurrence of influenzal meningitis.

SUMMARY

1. Recovery from influenzal meningitis, in which anti-influenzal serum and sulfadiazine had been used successfully is herein reported.

2. Although the patient was given 135.5 Gm. of sulfadiazine, there were no toxic effects.

3. Sulfanilamide and sulfapyridine had been previously used without clinical improvement.

The authors are deeply indebted to Dr. J. A. Kennedy of the Department of Bacteriology for his cooperation in presenting this paper.

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ORTHODONTIC PROBLEMS

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THE part which orthodontic therapy can play in facial contour and dental function is poorly understood not only by the medical profession and the laity, but also by dentists. At the time I entered the practice of orthodontics, the notion was prevalent that when teeth were moved into normal occlusal relation and held there, a rebuilding of the bony architecture of the face and consequent alteration in facial contour compensating for defective growth and hereditary pattern would be accomplished through function. The experience of orthodontists and the scientific research of Broadbent[1, 2] and Brodie[3, 4] have shown that there are limitations which must be placed upon what may be expected of the effect of tooth movement upon the form of facial skeletal architecture. Our present knowledge tends to emphasize the importance of hereditary pattern and the significance of prenatal and early postnatal handicaps to full growth and development of facial bones. These data need not depreciate the accomplishments of orthodontic therapy but serve to emphasize its usefulness within the limits of reasonable application. They contribute to more effective therapy and more intelligent prognosis.

The salvation of the orthodontist lies largely in the degree to which the alveolar bone is capable of answering the pressure stimuli transmitted to it by the teeth through their periodontal membrane attachment. Some of you may remember the emphasis which I placed upon this physiologic activity when discussing the significance of sucking habits with Langford[5] in Cincinnati. As mentioned at that time, the teeth represent relatively mobile units receiving pressure influence from their neighbors in the same jaw, their antagonists in the complementary denture, and the soft tissues about them. Through the periodontal membrane, these pressures are reflected upon the supporting alveolar bone which makes response depending upon the nature of the impulse, altering its structure to permit the teeth to resist the strain or decrease it by changing their position. This extremely important property of the alveolar bone contributes to normal facial growth and to the continual adjustment of the teeth to their complex environment. Under less favorable circumstances it permits the teeth to move into malocclusion when unable to resist abnormal pressures and to compensate for defective underlying osseous structure. Likewise it is the means of their response to orthodontic appliances.

While there are those who believe, with Breitner,[6] that changes may take place in the bony bases of maxilla and mandible, there is general agreement that the degree of adaptation in the following sites is in the

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order named: alveolar bone, temporomandibular joint, and bony base of mandible and maxilla. With no more satisfactory evidence than clinical observation and analogy in other osseous structures, I believe that external pressures as well as those of normal and abnormal function may affect the bony structure of maxilla and mandible and that this effect is proportionate with the degree of growth and developmental activity in the regions affected.

To group orthodontic problems according to the anatomic region affected may serve to clarify the intent of the foregoing remarks.

I. Deformities limited entirely or largely to the teeth and alveolar bone. Here the bony bases of maxilla and mandible as well as other craniofacial bones are essentially within normal limits of form and position.

II. Deformities primarily related to the bony bases of maxilla and/or mandible. In these cases the accomodating or compensating function of alveolar bone reflects these changes. The cranial base bones are less likely to show alteration with the possible exception of the glenoid fossa of the temporal bones.

III. Deformities primarily in the cranial base, with bony base and alveolar bone and teeth reflecting the disturbance secondarily.

More than one set of etiologic factors may operate upon a single patient in the course of his developmental progress, producing deformities in one, two, or all groups.

I. DEFORMITIES LIMITED TO THE TEETH AND ALVEOLAR BONE

Problems within this category include disturbance in the normal balance of the forces upon the teeth (for example, habits, loss of dental units, abnormal form or size of dental units, accidents in eruption, and occasionally abnormal position or orientation of tooth follicles). When the cause is no longer active or can be eradicated, they offer the most hopeful prognosis, because, as mentioned earlier, the orthodontist is able to exert his greatest influence upon the alveolar bone. These deformities may be very disfiguring, their correction dramatic, and the results enduring.

II. DEFORMITIES ESSENTIALLY WITHIN THE BONY BASES

When the deformity is primarily within the body of the maxilla or in the body or ramus of the mandible, the possibility of attainment of complete facial growth is less likely. While the degree to which a bone may eradicate the handicap of an arrest in growth is still a moot question with respect to maxilla, mandible, and temporal bones, the accumulated evidence to date seems to give little encouragement that there is complete compensation and that the severity of the insult, the developmental age of the bone, and the duration of the disorder are all significant factors in the extent of the permanent injury. I am glad to take refuge in the limited time available to avoid extended discussion of this point, for

reliable scientific data upon which to rest conclusions are extremely meager. Later I shall refer to the challenge offered to cooperative pediatric and orthodontic investigation by this intriguing growth problem. It seems reasonably certain that the vulnerability of the denture base bones bears a rough, if not absolute, relation to the rate of growth and that there are certain episodes in the activity of growth centers which are more sensitive than other periods in developmental progress.

If we are right in our conclusions with respect to the enduring effect of these handicaps, it is obvious that the burden of adjustment falls upon the structures more responsive to pressure stimuli. The alveolar bone and temporomandibular joint permit of certain elasticity in compensating for defective growth in the bony bases. This is true in unassisted cases as well as in those treated by the orthodontist. However, even these tissues have their limits, and prognosis must be governed by the severity of the deformity and the limits of the reactivity of the alveolar bone, glenoid fossae, condylar heads, and perhaps the remaining growth increment of maxilla and mandible.

In cases within this group the practitioner must often resort to repeated periods of mechanical stimulation throughout the growth period. His purpose is to assist and direct the compensating adjustment, particularly in the alveolar bone, and to obtain maximum constructive stimulation from an equitable balance in the functional forces which affect the facial architecture. Optimum rather than average health may mean the difference between success or failure in treatment in many patients within this group.

III. DEFORMITIES PRIMARILY WITHIN THE CRANIAL BASE

Fortunately for the reputation of the practitioner, orthodontic problems within this division are less frequent than in the foregoing. They may be confused with deformities of the base bones but are less often recognized. In the very fragmentary knowledge of the causative factors, it appears that the arrest is earlier in the developmental history of the individual and possibilities of restitution within the affected bones less likely. The effect of these deformities may be reflected in maxilla and mandible and commonly in alveolar bones and temporomandibular joint.

Compensation is effected as previously described, and prognosis must be guarded. In this, as in the second division, the orthodontist takes a child to raise. It is obvious that the diagnosis of these deformities cannot be made by observation of the teeth alone, nor can they be rectified by simply aligning the teeth in a symmetrical arrangement and holding them with rigid retainers. The only effective treatment at present is preventive, a good hereditary pattern and optimal health in the realization of that pattern. All else is in some measure a compromise. Yet a great deal can be accomplished in improvement of masticatory function and facial contour by capitalizing upon the alveolar bone response and assistance of oral and plastic surgery.

It is unnecessary to complicate this very abridged classification by introducing the combinations of the above deformities or by discussing the etiologic entities, both known and surmized, which may effect them. Enough has been said to indicate that orthodontic problems are more than straightening teeth and to explain why in cases of the first group a few months of treatment may effect a satisfactory and enduring result, while other periodic applications of therapy may only diminish and not eliminate the defect.

I cannot close without calling to your attention the very complex integration of growth and developmental factors combined in the facial architecture and their sensitivity to disturbance. If we were to consider other regions with the same standard of perfection in growth and functional activity as that demanded of the orthodontist, I have no doubt we would be similarly impressed. The parent may become reconciled to imperfection in stature, posture, or even latitude in weight. He will tolerate less than the greatest achievement in muscular development, and excuse a certain lack of perfection in organic function, but because the face is to such an important degree the avenue of expression and the center of attention in social contact, he desires perfection there. We can do a very credible job of nourishing children and adults with marked imperfections in jaw and dental structure, but we cannot give them perfect faces without the assistance of these tissues.

It is difficult for the layman to realize that optimum facial development is dependent upon the whole child. As an orthodontist, I am confronted with problems in attaining optimal growth and function which are above the level of given clinical significance in the average requirements of pediatric practice. That is why I make demands upon you for assistance in the minute details of nutrition, allergy, and systemic disturbance which you feel are a meticulous nuisance. I am not permitted the same latitude in facial growth that is granted in long bone growth.

In the end this annoyance may come to have more tangible value to pediatrics. Working upon the premise that failure to fulfill the pattern means disturbance in growth or function, or both, and given a knowledge of the pattern, an analysis of the defect may throw light upon the time, perhaps even upon the nature, of the insult. The development of this criterion may help us recognize deviation from optimal health which, when discovered and eliminated, benefits not only the face but the whole child as a functioning unit.

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American Academy of Pediatrics

Proceedings

ELEVENTH ANNUAL MEETING OF THE AMERICAN ACADEMY OF PEDIATRICS

BOSTON, MASS.—OCT. 8-11, 1941

Round Table Discussion on Therapy With Blood Substitutes in Childhood

Chairman: William Thalhimer, M.D., Director, Manhattan Convalescent Serum Laboratory, New York, N. Y.

Associates: Aims C. McGuinness, M.D., Philadelphia, Pa.
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DR. STOKES.—There is increasing interest in the use of blood serum and plasma, not only for therapy of acute contagious diseases with the immune bodies which they contain, but also as blood substitutes in emergency situations. These occur in civilian as well as in military life and have stimulated the development of the best blood substitutes.

Although Moon's mechanism of shock is generally accepted, some details and ramifications have not been completely worked out. A histamine-like substance may be involved in producing capillary injury, with loss of fluid from the capillary and vascular bed. The resultant diminished blood flow produces suboxidation of tissue cells, with further capillary dilatation, establishing a vicious cycle.

Under wartime conditions, immediate treatment of wounds and shock would be conducted at mobile battalion aid stations where the immediate administration of blood substitutes would often be a lifesaving measure. The wounded would be then sent back to the mobile field hospital, thence to a base hospital, where facilities for blood banks and whole blood transfusions would be available.

Three types of shock and injury are to be distinguished and may be present in varying combinations:

1. Generalized shock with blood concentration but with little or no hemorrhage.
2. Shock with a large blood and fluid extravasation into the tissues, but no external hemorrhage.
3. Severe external hemorrhage.

In type 1, the immediate indication in the first aid station is for administration of plasma, preferably concentrated, in an attempt to increase the circulating fluids and pull lost fluid back into the blood stream. Later, unconcentrated plasma or whole blood could be injected.

Solutions of purified albumin are of value for immediate increase in intravascular osmotic pressure. The purified albumin solution prepared by the method of Cohen, whereby the separate serum protein fractions are precipitated out by ethanol in buffered acetate at a temperature of −5° C., offers a solution of 30 Gm. of albumin per 100 c.c.

In type 2 injuries, undiluted plasma, if available, is best for immediate injection. If concentrated liquid plasma is not available, powdered serum or plasma, diluted immediately before administration, may be given. Under combat conditions, the powdered serum may be most feasible in the mobile first aid stations, with liquid serum and blood banks in the collecting stations and base hospitals.

In type 3 injuries, unconcentrated plasma or serum should be given immediately, then whole blood as soon as it is available. Other essentials of treatment for shock should not be disregarded.

In the treatment of burns, large quantities of blood substitutes may be necessary to replace protein and fluid loss from the burned areas. In extensive burns, 8 to 12 liters of serum may be given within four or five days.

Therapy With Blood Substitutes in Childhood

William Thalhimer,* M.D., New York City

The term "blood substitutes" has come to mean human serum or plasma in its liquid or dried form. It does not include solutions of salts and carbohydrates prepared for intravenous use. It might include preparations of human albumin, protein digests of various sorts, and other colloid solutions (such as gelatin or pectin). Although some excellent results have been obtained with these last-named materials, until more extensive clinical trial has proved their efficacy and their safety for intravenous injection, they should not be included under the term "blood substitutes."

My part in this round table will be mainly to discuss methods of preparing human serum and plasma in their liquid, concentrated, or dried forms, some of the general principles underlying their therapeutic use by intravenous injection, and some of the indications for these uses. The actual clinical use of these materials and the results obtained will be discussed by others.

Best and Solandt[1] have stated, "We wish again to emphasize the point that plasma and serum free from reaction-producing substances are physiologically and therapeutically identical and may be used interchangeably. It will be regrettable if discussion of the relative merits of these two materials should in any way impede their production or inhibit their use under appropriate conditions."

There are some differences between human citrated plasma and human serum which should be mentioned, and some of the difficulties which are met in processing or using these should be described.

Serum is the liquid part of blood which remains after whole, untreated blood has been allowed to clot and the clot and all cellular elements removed. It contains either no fibrinogen, or an insignificant trace, and it very rapidly loses thromboplastic substances.

Citrated plasma is the liquid part of citrated blood which remains after the cellular elements have been removed by sedimentation or centrifugation. It contains all of the original fibrinogen in solution, and it is not always possible to prevent fibrinogen from being deposited in the form of fibrin. It also contains thromboplastin in solution which is retained for a longer or shorter period of time.

For the preparation of either serum or plasma, blood is withdrawn by vein puncture with a rigid aseptic technique into a sterile bottle. This should always be carried out with a closed system. For the preparation of serum, the blood is drawn into dry, sterile containers, and then allowed to clot. For the preparation of citrated plasma, nine volumes of blood are added to one volume of citrate solution,

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the final percentage of citrate to be from 0.3 per cent to 0.5 per cent. Because of this 10 per cent dilution, the percentage of proteins in liquid plasma is less than in liquid serum.

It is generally agreed by all workers that fibrin in large or small amounts will form sooner or later in plasma stored in the liquid state. This is one of the disadvantages to the therapeutic use of liquid plasma and requires certain precautions in its intravenous administration. This danger from the use of serum does not exist.

Serum can be filtered with ease through a filter which will hold back bacteria, whereas plasma is filtered with difficulty. Furthermore, even when clear, filtered plasma is secured, in my experience there has been the great likelihood of the formation of large amounts of fibrin within from one to twenty-four hours. Some workers have introduced methods for the removal of fibrin in citrated plasma either entirely or almost entirely, but up to the present we have not been able to secure similar results. After the fibrin is removed from citrated plasma, the resulting preparation should no longer be known as citrated plasma, but should be called either serum or defibrinated plasma.

Because of this difficulty in passing plasma through a bacteria-proof filter, in most institutions this is not done, but reliance is placed on aseptic technique for maintaining the sterility of the plasma, and bacteriologic controls for proving its sterility. Whereas bactericidal or bacteriostatic substances are usually added, reliance must not and cannot be placed on these for sterilizing contaminated material. The bacteriologic tests for sterility should be observed for from one to two weeks, and it is, therefore, not safe to use plasma before the sterility tests have proved it to be sterile. In my opinion, neither serum nor plasma should be used unless possibly accidentally contaminating bacteria have been removed by filtration through the bacteria-proof filter. Also, it is my opinion that plasma or serum should be prepared only by a specially trained group in a separate self-contained laboratory devoted entirely to this work. Others disagree about this and believe that filtration is not necessary if accurate sterility tests are carried out.

In recent years, methods have been developed by Elser,[2] Flosdorf and Mudd,[3] and others to dry serum or plasma from the frozen state by means of a very high vacuum. These have been invaluable contributions, as properly dried serum and plasma will maintain their physical properties even at room temperature for a long period of time. Therefore large stores of these materials can and should be prepared for civil use as well as for use in emergencies, or in time of war.

Precautions should not be relaxed in proving the sterility of the dried preparations.

One method for preventing the formation of fibrin in plasma that has passed through a bacteria-proof filter is by introducing the filtered plasma into the final containers immediately after filtration and then immediately freezing. This frozen material can either be dried immediately or stored in the frozen state until there is an opportunity to dry it.

One other method of storing citrated plasma should be mentioned, and that is the procedure of Strumia[4] for freezing the plasma immediately and rapidly, maintaining the frozen state during storage, and thawing this in a warm-water bath at body temperature immediately before its administration.

We have devised and used a method for concentrating serum in liquid form to one-third its original volume in sterile cellophane bags. This is stored in glass vials or bottles.

Hartman[5] has devised an extremely interesting method for carrying serum or plasma to complete dryness in cellophane bags at atmospheric pressure and reports that he has had excellent results with the administration of this material when redissolved.

It has been found that when comparatively large pools of serum or plasma are prepared from bleedings from thirty or more donors belonging to the different blood

groups, in about the same proportion as these occur in the population, there is a great reduction in the titer of both anti-A and anti-B agglutinins. In our experience, the anti-B titer of these pools averages about 1-14 and the anti-A, about 1-28. It has been the general experience that blood substitutes with agglutinin titers as low as this can be administered in large amounts without any fear of damage from the injection of incompatible agglutinins, regardless of the blood type of the recipient. This is true when the agglutinin titer is low but might not be true when large amounts of material with a high agglutinin content are administered. Therefore, only blood substitutes with either a low titer or absence of agglutinins should be used. It is possible to remove all agglutinins by adding Witebsky's solution of A and B substance to pools of serum or plasma.

Therefore, as can be seen, there is no danger from the injection of properly prepared pools of serum or plasma even though they contain some incompatible agglutinins. This is entirely different from the extreme danger of administering, through error, of course, an incompatible blood transfusion where the incompatible blood cells always cause severe reactions and, not infrequently, death.

In addition to the advantages already stated of dried serum or plasma, there are other advantages as well. When distilled water is added to this dried preparation just before use, it redissolves very rapidly, usually within a few minutes. It can be made up to the original volume and will then be isotonic, or only enough water can be added to make it up to as little as one-fourth its original volume when it can be administered, if indicated, in this concentrated form.

Properly prepared serum, either in its liquid form or when dried and redissolved, can be administered intravenously without placing a filter in the intravenous outfit. It is generally agreed that either liquid plasma or redissolved dried plasma should always go through either a gauze, absorbent cotton or a finely meshed metal filter immediately before it is introduced intravenously. This filtration is necessary either to prevent the introduction into the patient's circulation of bits of fibrin, which may form in the plasma, or to prevent the bore of the needle from being stopped up by fibrin. It has been stated that this filtration is not necessary with reconstituted, dried, or frozen citrated plasma. I cannot help but feel that one should always play safe and introduce filtration at the time of intravenous administration of plasma, no matter what its source.

One advantage to the use of plasma is that it can be prepared from citrated blood stored in blood banks after the time has expired when the blood can be used with safety for transfusions. The supernatant plasma can be salvaged, processed, and used as a blood substitute.

There is some difference of opinion as to the likelihood that the intravenous administration of sizable amounts of serum or plasma will result in fever-chill reactions. It is stated by some that they either never or rarely have seen reactions from either one of these materials. Others have found from 5 to 10 per cent, or even more, reactions from each of these materials. It is difficult to account for this difference in experience, and it is difficult to believe that no reactions at all will occur. Even with careful technique and with the best care of apparatus and the most careful preparation of physiologic saline or glucose solutions, there will always be at least an occasional reaction if these materials alone are administered intravenously often enough. Certainly, however, the reactions which follow the intravenous injection of any of the preparations of blood substitutes are not more frequent and not more severe, in fact, possibly less so, than those following well-checked, careful, whole blood or citrated blood transfusions. With the intravenous injection of blood substitutes, there is no possible danger from the injection of cellular elements, as in blood transfusions, especially if the blood substitute material has been passed through a bacteria-proof filter. Since one does not hesitate to administer blood transfusions when

they are indicated, one should hesitate still less to use blood substitutes when the use of these is indicated.

The chief proved field of usefulness for blood substitutes at present is in the treatment of traumatic or postoperative shock, and also for the immediate emergency treatment of large blood loss. Other conditions for which blood substitutes are being used are the treatment of hypoproteinemia from various causes, treatment of diarrhea or intestinal intoxication in infants, the treatment of patients with severe burns or burn shock, and patients in the early stages of pure lipoid nephrosis.

Moon[6] distinguishes between shock and the condition which results from massive blood loss. He has demonstrated that one of the earliest signs of oncoming shock is hemoconcentration, meaning that a larger percentage of cellular elements are present in a given volume of blood and a small percentage of plasma with, in all probability, diminution of the entire blood volume. Hemoconcentration, he has found, occurs before there is any detectable fall in blood pressure, and that, as a matter of fact, a fall of blood pressure indicates that shock has been developing for some time and is already at an advanced stage. The reason for hemoconcentration is believed to be because the capillary bed is injured and cannot hold water and proteins within the blood vessels, thus allowing them to pass out into the tissue spaces. With diminished blood volume and increased viscosity of blood, the heart has difficulty in maintaining circulation; anoxemia follows, further diminishing the functional capacity of the heart, setting up a vicious circle which, if not interrupted, will go on to extreme shock and death. It is not only necessary to introduce fluid into the circulation, but it must be fluid of a type which will stay in the circulation and not seep through the endothelium of the capillaries into the tissue spaces. Physiologic saline solutions, solutions of glucose and other saline-carbohydrate solutions, under these conditions, will stay in the circulation only a short time. The beneficial effect is transitory. Whole blood transfusions in shock sometimes do more harm than good because with the administration of the cellular elements, hemoconcentration is increased rather than decreased. It has been found that the best treatment is the intravenous injection of plasma or serum. These normal, human colloids have a greater tendency to stay in the circulation than other materials, therefore maintaining the increase in blood volume longer, with a more sustained maintenance or increase in blood pressure, and with a greater likelihood that recovery will follow. If there has been no loss of blood, and if there is a large amount of fluid in the tissue spaces, concentrated serum or plasma should be injected intravenously. This will cause an increase in osmotic pressure within the blood vessels and actually cause the withdrawal of extravasated fluid from the tissue spaces back into the blood vessels, an ideal sequence. When the patient has lost water by sweating or evaporation from the lungs, or by diarrhea, isotonic and not concentrated serum or plasma should be administered.

The results of the treatment of shock that have been reported from England have been most encouraging. Many lives appear to have been saved which otherwise would have been lost. It has been startling, however, to learn that what previously would have been considered huge amounts of serum or plasma must be injected intravenously in order to produce the necessary beneficial effect and are now considered routine treatment. It was formerly thought, I am sure, that one should expect an excellent response in shock from the intravenous injection of 500 c.c. of serum or plasma. Many cases have been reported where the patients have had to receive huge amounts, sometimes as much as 3 or 4 liters in twenty-four to forty-eight hours, or 8 or 10 liters in four to five days.

It has also been found that multiple injections of from 500 to 1,000 c.c. must be given to adults at short intervals of four to eight hours. Therefore, children in shock undoubtedly should receive comparable amounts corresponding to their body

weight when they are in shock, or when they are suffering from severe burns. It has been found that this type of therapy in an individual with burns not only results in general clinical improvement, but also causes diuresis at times when kidney function is much reduced or has stopped.

Discussion of the treatment of hypoproteinemia in children and pure lipoid nephrosis will be left to others.

These blood substitutes have been found to have an extremely important place in the immediate treatment of large losses of blood. It has been found, in experimental animals, that most animals who have had removed, while under an anesthesia, from 40 to 60 per cent of their total blood volume, and if untreated or given saline or glucose solutions intravenously would die, will recover if immediately at least 40 per cent of the amount of blood lost is replaced by isotonic serum or plasma. The same has been found to be true with human beings who have lost large amounts of blood.

There is the advantage that a supply of these blood substitutes can be kept on hand and can be administered intravenously within a few minutes, because this material can be given with safety without regard to the blood type of the individual. The administered incompatible agglutinins disappear from the recipient's circulation within a few minutes.

During the period of improvement which follows, preparation for blood transfusions can be made, to be administered if excessive hemorrhage occurs. This reduces the hazards of performing incompatible transfusions because of pressure of time and urgency. The problem of the safety of universal donors for transfusion purposes in emergencies need not be discussed here, as we are discussing only blood substitutes, and this has been discussed many times elsewhere.

The experience with these blood substitutes already has been sufficient to demonstrate that they really can be considered, under many circumstances, to be an excellent substitute for blood transfusions, and, in some conditions, are to be preferred. They can be considered as "substitutes for blood" within the limits mentioned.

There are other conditions where logically they can be considered to be an important therapeutic measure. Some of these are treatment of patients with severe colitis and excessive loss of fluid and proteins; individuals with severe peritonitis, with removal of large amounts of protein from the blood stream into the peritoneal cavity; acute or chronic empyema of the thorax with similar removal of protein from the blood; undernourished children who refuse to eat properly; reduction of excessive intracranial pressure by the intravenous injection of concentrated blood substitutes. Other fields of usefulness may occur to many of you.

The quite extensive experience up to date has certainly demonstrated the importance of the use of blood substitutes. The ease with which they can be stored, their keeping qualities, and the rapidity and safety with which they can be administered should lead to an intensive, widespread plan for securing large supplies of these blood substitutes in many parts of this country, so as to have these available not only for use in civil practice, but also for large-scale emergency use in times of possible disaster or war.

It is impossible to end without urging that the start that has already been made be expanded greatly to secure a large supply of blood substitutes, since even under the best circumstances, with aid from the government, the Red Cross, and various special laboratories, it will take time to accomplish this.

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DR. McGUINNESS.—It is worth bringing up the mention of the various types of apparatus for drying serum. They all date back to the idea of Shakell, who first suggested the drying of serums, and which was developed later by Elser of Cornell. The final development was by Mudd and Flosdorf at the University of Pennsylvania. The serum was evaporated to dryness in the frozen state at a temperature of -78° C. The difficulty with the initial lyophile process was its cost. Flosdorf therefore developed the cryochem process which depends upon the use of a chemical desiccant and self-freezing by means of rapid evaporation.

There is also the adtevac process of Hill which uses a silica gel, and the dessivac process of Flosdorf which eliminates the condenser and uses what may be described as a reverse cream separator. The cost of this apparatus, however, is $5,000, which is of course a disadvantage for a small laboratory. The lyophile and dessivac processes are the most practical for commercial units, while the adtevac or cryochem is suitable for smaller establishments.

There have been reactions from vacuum-dried materials and we in Pennsylvania were responsible for spreading the first great scare. Dr. Stokes and Dr. Aldrich were responsible for the development of interest in the treatment of nephrosis. We were getting very unfavorable reactions and we stopped its use until we subsequently found that it had something to do with the method of handling the material, particularly the storage. Since this has been corrected and the difficulties eliminated, we have no more fear.

Application in Pediatrics.—One thing has to be stressed, whether we are to use hyper- or isotonic material. Whenever there is blood loss, the need is for fluids. Where there is shock with damage to the capillary walls and seepage, hypertonic solutions are of value. In pediatrics, serum or plasma may be used in pyloric stenosis, in poor healing of wounds, and in undernourished children. Burns represent a tremendous field of usefulness. In dehydration with hemoconcentration, where the blood count is six million or more, one would not dare to give blood transfusions, but serum or plasma, on the other hand, may be very useful.

In nephrosis, Aldrich and we were excited about treatment with four times concentrated plasma. In our first cases the edema faded like dew before the morning sun. Where there was microscopic hematuria, elevated blood pressure, or an increase in the cellular concentration of the urine, there was usually no response. It is a very expensive therapy and should not be wasted on this type. Better results are obtained in the early cases of nephrosis when there are no cellular elements or hypertension.

As to the nature of the response, this is entirely speculative. It cannot be due to the amount of protein given, as it is not sufficient to raise the serum protein above the edema level. However, children who do respond will do so on this small amount of added material. This suggests a trigger mechanism which may be set up by the administration of such small amounts. One is rarely able to measure a significant increase in serum protein.

It is well to mention briefly the work of Dr. Edwin Cohen who, by alcoholic fractionation, was able to get out the albumin fraction. There is a feeling that this may be helpful in the treatment of traumatic shock. It is relatively reactionless. This work is considered so important that a secrecy order has been placed upon it by the American Government.

DISCUSSION

CHAIRMAN THALHIMER (Demonstrating a 1 liter pyrex centrifuging bottle).—This is the 1 liter bottle which we use for freezing and drying. It contains 500 c.c. of plasma which has been dried. We use the simple inexpensive apparatus designed by Folson which costs between $300 and $400, including the pump.

DR. JEROME GLASER, ROCHESTER, N. Y.—How do you sterilize cellophane and does it stand autoclaving? How often do urticaria or other allergic reactions follow injection of blood substitutes?

DR. G. M. CLINE, BLOOMINGTON, ILL.—Do allergic reactions occur with these blood substitutes?

CHAIRMAN THALHIMER.—We autoclave cellophane. It stands autoclaving very well and dializing very well.

Urticaria and mild serum sickness from the intravenous injection of convalescent serum occur in about 0.5 per cent of individuals. Since the proteins are undenatured in dried serum, the same percentage of reactions would apply to both. The urticarias are mild and are not accompanied by joint pains. There have been no immediate severe allergic reactions. There is occasionally a temperature rise to 101 or 102°.

DR. McGUINNESS.—We have seen a few severe allergic reactions in the past eight years.

CHAIRMAN THALHIMER.—Some undenatured protein might be absorbed from the gastrointestinal tract and be present in the individual's serum.

DR. S. F. RAVENEL, GREENSBORO, N. C.—May the role of potassium in its production and maintenance be disregarded if enough plasma or serum is given in shock?

CHAIRMAN THALHIMER.—So far as I know, there have been no studies on this point.

DR. RAVENEL.—What is the best practical method of determining hemoconcentration and impending shock?

CHAIRMAN THALHIMER.—The total protein in plasma or serum can be rapidly calculated by the falling drop method. The hematocrit method is satisfactory for determining relative cell volume. Failing these a blood count can be of value.

DR. RAVENEL.—What about the use of adrenal cortical extract?

DR. McGUINNESS.—I think that good enough results may be obtained from serum or plasma alone.

DR. RAVENEL.—Is it not much cheaper and just as effective to give babies with pyloric stenosis or with moderate hypoproteinemia blood transfusions instead of plasma or serum?

DR. McGUINNESS.—It is not as effective because babies with pyloric stenosis are not anemic but rather dehydrated and hemoconcentrated, and for that reason it is wiser not to give extra blood cells.

DR. RUSSEL C. BOND, WHEELING, W. VA.—In a plasma bank using the Baxter apparatus, is there any advantage in the two methods used to get plasma; that is, is there any difference between the centrifugal method and the method of sedimentation by standing?

CHAIRMAN THALHIMER.—The method of standing is preferable in small institutions.

DR. McGUINNESS.—Small hospitals without a blood bank or a laboratory should not be prevented from using plasma. It is often handled in a rather crude way and I know of one fatality in a large hospital. I cannot overstress the care which must be used. Often blood that has been standing around unused has the plasma salvaged, and this is a chance for considerable trouble unless the handling is very careful.

DR. R. L. JACKSON, IOWA CITY, IOWA.—I agree with Dr. McGuinness. We who have used blood substitutes clinically are impressed with the need for statistical analysis in such diseases as empyema, rheumatic fever, and tuberculosis. I have seen improvement frequently when it had been used in fairly large amounts. I should like to stress its use in undernourished children with low-grade infections, from a nutritional standpoint. I have seen dramatic results with lyophile concentrated serum when the patient's cellular elements were increased and there was hypertension, but I agree that the prognosis is poor and question if it is economically sound. If the case is late, it has been our experience to find some enlargement of the liver to make one feel that one is dealing with liver pathology.

DR. FAIRFAX HALL, NEW ROCHELLE, N. Y.—What is the cost to the practitioner?

CHAIRMAN THALHIMER.—We are not yet producing for general use. Sharpe and Dohme are charging the doctor approximately ten cents per cubic centimeter, or $26.60 for 250 c.c. Cutter and Baxter both charge $25 for 250 c.c. of liquid plasma. In our own laboratory, which is not a profit-making organization, I think we could produce it at the cost of six cents per cubic centimeter. Even so, it would cost quite a bit when large amounts have to be considered. Nevertheless it is important that it should be produced for hospitals that cannot produce for themselves.

DR. GLASER.—What about cadaver blood?

CHAIRMAN THALHIMER.—We have had no experience with it.

DR. BOND.—What about placental blood?

CHAIRMAN THALHIMER.—When used properly, it is probably all right.

DR. McGUINNESS.—Placental blood is almost impossible to obtain unhemolized. Then again we must remember that every cubic centimeter of placental blood that we take means that much taken from the baby. Placental extract, it must be remembered, is not plasma. It is only the globulin fraction of adult serum.

DR. ALTON GOLDBLOOM, MONTREAL, QUEBEC.—During all my work on icterus neonatorum, I had never once succeeded in obtaining a sample of placental blood that did not show a tinge of hemolysis, no matter how soon after obtaining it, it was separated.

CHAIRMAN THALHIMER.—We were always afraid of producing plasma or serum with a tinge of hemoglobin. I think hemoglobin in citrated blood is an unpleasant thing, for it frequently means contamination. Hill, in Dallas, Texas, turns out dried defibrinated plasma, markedly colored by hemoglobin, and he states that it has been given intravenously without reactions. The hemoglobin present in his preparation is present because he pools bloods regardless of grouping, and hemolysis is possibly caused by the isoagglutinins which are mixed in all these groups.

Ottenberg and Fox and Keith Cannan have produced hemoglobin itself to see if it does good or harm. Cannan has injected up to 8 Gm., I believe, of pure hemoglobin

without evil results. After 8 Gm. it spills over in the urine. They have had no experience in shock but their objective is to see if cells can be salvaged and the hemoglobin in solution be used as a blood substitute.

DR. McGUINNESS.—How does Dr. Thalhimer feel about the presence of large amounts of fat in these materials?

CHAIRMAN THALHIMER.—We like to get the material as free from fat as possible, but the donors do not play the game and do not refrain from eating before they come to the laboratory. However, after filtration our serum is clear.

DR. McGUINNESS.—We get fewer faintings if the donors have had something to eat, but paid donors cannot be made to come in on an empty stomach. Most observers feel that the only difference is in the appearance of the plasma.

DR. BOND.—We have ours come in before breakfast.

DR. McGUINNESS.—We are bleeding donors all day long. It is therefore too difficult to bleed most of them on an empty stomach.

CHAIRMAN THALHIMER.—What happens with the withdrawal of fluid when concentrated serum is given? Weech and Lyttle found an increase of 25 per cent in blood volume in ten to twenty minutes when there were large amounts of fluid in the tissues of nephritic children.

DR. McGUINNESS.—It can be done rapidly. In the acacia days, one boy had a blood pressure of 100/50. In twenty minutes the blood pressure was over the top of the monometer. He was saved by a prompt phlebotomy. This should serve as a warning.

DR. GLASER.—What about its use in cerebral edema?

CHAIRMAN THALHIMER.—I have suggested hypertonic serum in cases of bulbar poliomyelitis and pulmonary edema. It seems to me that since some patients with bulbar poliomyelitis do recover and some of the extensive initial paralysis is explained on the basis of edema, relief of edema in the temporary paralysis of bulbar poliomyelitis is of great importance.

We must steer a conservative course in the development of blood substitutes. We have to be very careful not to use it as a shotgun and overdo it. It has become necessary now to instruct people not to overuse it.

DR. F. H. VON HOFE, East Orange, N. J.—Is there any advantage of serum over plasma? What was the rationale of selection of undernourished children who were benefited by injections of serum?

CHAIRMAN THALHIMER.—Serum and plasma apparently are of equal benefit to the patient. Plasma must be filtered during administration to remove any fibrin particles which might occlude the needle.

The undernourished children mentioned were hospital inmates with definite hypoproteinemia and showed decided general improvement after receiving blood substitutes.

DR. VON HOFE.—How does one determine what dosage of serum should be given?

DR. STOKES.—Doses should be not too large and should be frequently repeated, depending on the patient's needs, as determined by hematocrit estimation, blood protein levels, and the clinical response.

Experience in England has shown that in the treatment of severe wounds, serum may have to be diluted with saline or dextrose solutions in order to afford ample

fluid replacement. The child who has high fever and dehydration is burning his body tissues, with resultant high urea excretion. Large amounts of fluid are necessary for the elimination of these nitrogenous products, as well as electrolytes, such as chloride. For this reason, it may be necessary to use large containers in preparation of blood substitutes so that extra amounts of fluid may be added if indicated.

DR. H. H. DONNALLY, WASHINGTON, D. C.—How many grams per cent would you consider as hypoproteinemia?

CHAIRMAN THALHIMER.—Anything less than 7 Gm. per 100 c.c.

DR. STOKES.—The estimation of hypoproteinemia depends on whether there is a loss of total protein or certain protein fractions. Patterns of protein fraction analyses in disease processes show that separate fractions may be involved in antibody production or levels.

DR. J. V. GREENEBAUM, CINCINNATI.—What is the time limit for the preservation of dried plasma? Could plasma be used subcutaneously or intraperitoneally in urgent cases?

CHAIRMAN THALHIMER.—According to present knowledge, dried serum or plasma may be preserved from one to several years. Liquid plasma is absorbed rapidly from the subcutaneous tissues or peritoneum, but it is more advantageous to give it intravenously in urgent cases.

DR. GREENEBAUM.—Should it be fully diluted if given intraperitoneally?

CHAIRMAN THALHIMER.—So far as I know, no one has used concentrated serum intraperitoneally. However, scarlet fever antitoxin (horse serum) has been given intraperitoneally.

DR. R. M. LORD, PROVIDENCE, R. I.—Is casein hydrolysate considered in the classification of blood substitutes?

CHAIRMAN THALHIMER.—Dr. Whipple and his group did not consider casein hydrolysate as a blood substitute. It cannot be depended upon as an immediate counteractor to shock, but within a day or two after its intravenous administration it helps to build up the proteins.

DR. STOKES.—Metabolic experiments are favorable to its use. Slight reactions may occur.

DR. J. H. FRIES, BROOKLYN, N. Y.—Is there any alteration or diminution of antibody or antitoxin content in the process of drying or freezing blood plasma?

CHAIRMAN THALHIMER.—There is no demonstrable effect on antibodies from freezing and drying.

DR. STOKES.—Complement is preserved after drying and this is the most labile of all antibodies. Others show no deterioration over a long period of time if the material is kept on ice. At room temperature or higher, some deterioration occurs.

DR. DONNALLY.—Is human plasma of benefit to premature infants and how often should it be administered?

DR. STOKES.—It is of great value for premature infants but may be difficult to give intravenously. Administration must depend on tests and clinical improvement.

DR. DONNALLY.—It may be given by scalp vein or by subcutaneous injection. It does not help the anemia of premature infants.

DR. C. V. CALVIN, BRIDGEPORT, CONN.—Is the main reason for filtration to remove bacteria?

CHAIRMAN THALHIMER.—Yes, also to remove any gross particles which might stop the needle or act as emboli.

DR. R. W. HOLT, NIAGARA FALLS, N. Y.—Is it true that syphilitic or other infected bloods can be used indiscriminately for blood plasma and are rendered safe by the processing method?

CHAIRMAN THALHIMER.—Theoretically, such blood is safe, especially after it is passed through a bacteria-excluding filter. However, no bloods are used which show as much as 1 plus Wassermann or precipitin reaction.

DR. STOKES.—Flosdorf and Mudd have injected serum from syphilitic individuals, prepared in the standard manner, into rabbit testicles and were unable to produce syphilis. It would appear that all of the methods used for preparation of blood substitutes remove spirochetes, even if a mistake in blood testing were made.

DR. DONNALLY.—Do whooping cough convalescent serum and hyperimmune serum produce beneficial effects in treatment of the disease?

DR. STOKES.—The average convalescent from whooping cough has an agglutinin titer of 1 to 300, whereas the hyperimmune serum as prepared by Dr. McGuinness has a titer of 1 to 2,500 or more. For this reason the latter is advocated. The mouse-protecting method is probably the best means available for determining the value of a given serum.

At the Children's Hospital in Philadelphia, results in prevention have been very successful, especially in infants, where 25 to 50 per cent complete protection has been secured.

DR. DONNALLY.—How much hyperimmune serum should be given?

DR. STOKES.—For the infant under 6 months of age, 30 c.c., repeated in two days.

DR. W. A. McGEE, RICHMOND, VA.—The reported mortality of pertussis in infancy does not hold true in private practice. I have seen only one death in 400 cases in private practice.

DR. G. J. LEVY, MEMPHIS, TENN.—This is not the case in our experience and certainly not in institutional cases.

DR. R. C. HOUGH, SAN DIEGO.—In pediatric practice, the most important use of plasma is in burn shock and nephrosis. Please discuss treatment of these conditions, giving mathematical formula for calculating protein replacement.

DR. STOKES.—An exact mathematical formula would be difficult to state. However, if we secure the total serum protein level, the difference between this and the normal level gives the protein deficit in grams per cent. If we then consider one-tenth of the child's weight as blood volume, approximately one-half of which is blood serum, then we can calculate the amount of protein and of serum which needs be given.

In the treatment of nephrosis with serum, Aldrich has shown that some cases respond quite favorably. Results in Philadelphia have not been quite as good as reported by Aldrich, and it is possible that his results are explained by a very careful selection of cases for this form of therapy.

The mechanism whereby some patients with nephrosis improve dramatically after serum administration is not known. Farr thinks that the answer may lie in a

study of the amino acids. It is also possible that a sudden increase in blood volume, with decrease in tissue fluids due to altered osmotic pressure, may set off a trigger mechanism which stimulates renal excretion.

DR. THALHIMER.—Little and Weech find that concentrated serum injection causes withdrawal of tissue fluids into the circulation with startling rapidity. If the kidneys are in a position to excrete fluid, this also may occur rapidly; if not, very little result is seen.

The adult with albuminuria and severe hypoproteinemia requires 1,000 c.c. of serum to increase the level of his blood proteins by 1 per cent.

DR. W. E. KEITER, KINSTON, N. C.—Will the mortality in burns be reduced materially by serum therapy?

DR. THALHIMER.—In the experience of a few investigators who have given serum in large amounts, yes.

DR. DONNALLY.—Hyperproteinemia can be produced by prolonged serum administration.

DR. THALHIMER.—It is necessary to follow the blood protein levels and thereby avoid the risk of excessive serum administration. However, there is more likelihood of too little, rather than too much, serum being given.

DR. W. E. VAN ORDER, CHATTANOOGA, TENN.—Is it necessary to type the blood before giving the serum?

DR. THALHIMER.—If pooled serum or serum from individuals of different blood groups is given, then both A and B are present, with antigens against isoagglutinins. It has been found in several groups of children that immediately after pooled serum was administered intravenously, (1) no incompatible agglutinins were present in the patient's blood, and (2) there was absolutely no agglutination of the patient's circulating cells. Caution must be taken that serum have a low agglutinin titer.

DR. VON HOFE.—May one feel secure against the R H factor?

DR. THALHIMER.—Danger of injury from the R H factor is not present from the administration of serum. Blood cells must be introduced to have an R H reaction. I feel that it is safe to disregard a low titer of incompatible agglutinins in injected serum.

DR. McGEE.—If serum is taken from soldiers who have had tetanus toxoid and is given to wounded men, would this provide protection against tetanus?

DR. STOKES.—This depends on the level of antitoxin in the donors' bloods.

DR. THALHIMER.—The blood antitoxin level after three injections of tetanus toxoid averages only 1 to 2 units per cubic centimeter, although an occasional individual has 25 to 50 units per cubic centimeter. The minimal dose of tetanus antitoxin for the adult should be 1,500 to 3,000 units, so that a total of 2,000 to 3,000 c.c. of serum would need to be injected to assure full protection against tetanus.

DR. STOKES.—It should be noted that it is possible to produce severe reactions by injecting tetanus toxoid repeatedly.

ELEVENTH ANNUAL MEETING OF THE AMERICAN ACADEMY OF PEDIATRICS

BOSTON, MASS.—OCT. 8-11, 1941

Round Table Discussion on Urologic Conditions in Children

Chairman: Meredith F. Campbell, M.D., Professor of Urology, New York University College of Medicine; Associate Attending Urologist, Bellevue Hospital, New York, N. Y.

Associates: Thomas H. Lanman, M.D., Assistant Professor of Surgery, Harvard Medical School; Visiting Surgeon, Children's Hospital, Boston, Mass.
John D. Lyttle, M.D., New York, N. Y.

Secretaries: Herman M. Jahr, Omaha, Neb.
Joseph Yampolsky, M.D., Atlanta, Ga.

The Indications for Urologic Examination in Children

John D. Lyttle, M.D., New York City

A complete urologic examination includes special analysis of the urine and blood, roentgenograms of the urinary tract, urethroscopy, cystoscopy, cystometry, cystography, urethrography, ureteral catheterization, retrograde and intravenous pyelography. It may be necessary to test the function of each kidney separately. Some of these procedures can be carried out by the practitioner, but it is generally better that the plan and extent of the urologic investigation in each case be made with the cooperation of the urologist. It is important to emphasize that the interpretation of the findings and the management of the patient is the joint responsibility of the pediatrist and the urologist.

The following conditions are listed, approximately in the order of their importance, as indications for partial or complete urologic investigation: pyuria, disturbances of urination, hematuria (except acute nephritis), abdominal pain, abdominal tumors, spinal cord injury and disease, anomaly of external genitalia, hypertension, renal insufficiency, enuresis, and retarded growth.

Taking these headings in the order given, everyone will agree that persistent or recurrent pyuria indicates stasis and requires investigation. Many cases of pyuria are found to be associated with urinary tract anomaly or obstruction. In the past, it must be admitted, with older methods of treatment it was often difficult or impossible to eradicate infections in this type of case. As pointed out by Helmholz, however, it is now possible to clear up infection in the presence of stasis in the urinary tract and Helmholz concludes that some technique of visualization of the urinary tract, at least intravenous urography, should be carried out in every case of urinary infection as the only way to discover anomaly or obstruction before serious kidney damage occurs. This may seem an ideal difficult to achieve, but the follow-up studies of pediatrists and internists show that no other position is tenable.

By including disturbances of urination among the indications for urologic examination, I do not mean to pick on the boy who occasionally wets his pants when suddenly terrified. I mean to signal out those symptoms of lower tract involvement, such as dysuria, frequency, urgency, and dribbling. If these symptoms persist, a cause must be found.

There is no such condition as "essential hematuria," and except in the presence of systemic disease, as scurvy, hemophilia or Bright's disease, all children whose urine contains blood should be investigated.

With regard to the other indications it is obvious that not all children who have these conditions need be subjected to complete investigation. The analysis of our case material shows that a careful study of the history, a physical examination, and laboratory findings will usually determine the question. Urologic kidney disease is not the only cause of high blood pressure. In children it is a very common cause. In some children with abdominal tumor and abdominal pain, the history and physical examination may at once rule out the kidney. No hard and fast rule can be made, but in any child with recurrent abdominal pain, undiagnosed, the urinary tract deserves careful appraisal. One of our patients with hypospadias was found to have an ectopic kidney. What led to the investigation was the fact that in addition to the hypospadias he had developed hypertension. Statistics show that approximately one-third of the individuals with anomalies of the external genitalia will show upper urinary tract anomaly. Nocturnal enuresis in the great majority of instances is functional. When it does not yield to adequate medical treatment, including suggestion and other psychotherapeutic measures, or when it persists in older children, urologic examination must be considered. When the cause of retarded growth and development is not obvious, particularly when late rickets is present, kidney damage must be considered as a possibility.

Chronic glomerulonephritis is one of the great scrap baskets of renal diagnosis. This term covers a variety of urologic conditions which have nothing in common with true chronic glomerulonephritis except renal insufficiency. A careful study of the patient's history and a physical examination may lead one to suspect urologic disease. These patients rarely show edema or changes in the serum proteins. Hypertension is frequently present early in the course. A history of recurrent urinary infection is a significant finding. Early the urine may show only moderate albuminuria and pyuria; later polyuria and hyposthenuria may be added. But the course may be symptomless until uremia develops. The importance of differential diagnosis lies in the fact that early diagnosis may reveal some cases that are amenable to surgical treatment.

The importance of urologic conditions should need no emphasis before this group. The frequency of urinary tract anomaly in children is well known. It has been found to be as high as 15 per cent in some series of autopsies. The close association of severe renal inflammatory and degenerative processes, acute and chronic, with urinary tract anomaly is also well recognized. The pathology of urinary infection was first carefully studied by pediatrists. But I think we owe a debt to the urologist and internist who followed our children many years after they had passed through our hands. They were frequently able to trace the slow insidious course of the process over the long intervals during which it was clinically silent. They brought out the fact that some cases of "chronic Bright's disease," "essential hypertension," and uremia occurring in young adults had their beginning in a congenital anomaly, or the "pyelitis" of infancy.

It does not lessen the importance of our problem to admit that not all children who have urinary tract anomaly or infection or both are destined to develop hypertension and uremia. The fact that in the course of our investigations we may discover conditions which at the present time are apparently irremediable should not discourage us. Our obligation is clear. Our objective is to discover these conditions at the earliest possible time, so that in conjunction with the urologist all possible steps may be taken to prevent the development of irreversible changes in the renal and vascular system.

Conditions in Children Which Result in Incontinence and Dribbling

Thomas H. Lanman, M.D., Boston

I wish to discuss more in detail certain of the conditions to which Dr. Lyttle has referred, paying particular attention to those conditions which result in incontinence

and dribbling. Not uncommonly these two symptoms are referred to by the loose and dangerous term "enuresis." Never forget that enuresis may be the incontinence and dribbling of the obstructed and overdistended bladder. It is of the greatest importance that physicians be on the lookout for obstructions that result in incontinence, especially during the diaper-wearing age. Unless great care is exercised, the patient may be regarded as a training problem for many months or even years after the age they are expected to acquire urinary control.

Obstructive Lesions.—The obstructive lesions that cause incontinence and dribbling are by far the most important in that severe kidney damage will result unless the obstruction is recognized and relieved at an early date. There are several types. Those of the external genitalia and urethra include such conditions as hypospadias with a very small urethral opening; developmental conditions of the urethra itself, such as stricture or diverticulum; and in the older age groups, stricture resulting from trauma. Urinary obstruction due to phimosis is rare but can occur; it is easily recognized and treated.

One of the most insidious and dangerous types of urethral obstruction is that caused by congenital valves in the region of the verumontanum. There is no obstruction to the passage of a catheter, but the hydrostatic pressure of the urine on voiding tends to close the valve tighter and tighter. This condition often results in a much thickened, trabeculated bladder and in enormous dilatation of the ureters and kidneys. The clinical picture of the advanced case is very similar to that of a patient suffering from prolonged obstruction by a hypertrophied prostate. There is a constant dribbling from the overdistended and obstructed bladder, a tremendous degree of nitrogen retention, and severe kidney damage.

This congenital defect is extremely likely to go unnoticed, because this type of incontinence is not differentiated from that of the normal untrained infant. The child is not expected to have urinary control in his early months. It is potentially one of the most dangerous conditions, in that severe and irreversible renal damage may take place before the obstructive element is recognized and submitted to surgical relief.

Other less common lesions include tumors of the bladder itself, or tumors of other organs pressing on the urethra, such as cysts of the vagina, particularly hydrometrocolpos. Tumor masses within the bladder that are not new growths, such as large ureteroceles of either or both ureters, must be considered. A ureterocele may become so large as to obstruct the vesical outlet.

Nonobstructive Lesions.—Nonobstructive lesions are less dangerous in that they may not cause any back pressure on the kidney, but nevertheless they should be recognized and treated early. Incontinence which persists after two or three years of age in spite of everything that can be done as regards training may be caused by an ectopic ureter which empties distal to the bladder sphincter, most commonly in the urethra itself. This condition once recognized can be treated surgically in several ways with complete relief of symptoms.

Any case of enuresis should have careful neurologic as well as urologic examination, as there are several conditions which will cause an atonic "cord bladder" with incontinence. Among these are trauma, spina bifida occulta, and tumors pressing on the lower lumbar sacral cord. Foreign bodies in the bladder are rare, but we have had instances where a foreign body introduced in the bladder resulted in a vesicovaginal fistula that went unnoticed for several years. Anomalies of the urachus, particularly when associated with stone formation, may cause urgency and an apparent incontinence.

In general, it must be borne in mind that any case with disturbance of urination demands a careful and painstaking investigation not only from the psychiatric viewpoint but, much more important, from the urologic and neurologic viewpoint.

A child with some form of urinary incontinence is too often treated as a "behavior problem."

Exstrophy of the Bladder, Epispadias, and Hypospadias.—Exstrophy of the bladder results in total incontinence. At the Children's Hospital we have had great success in these cases by transplanting the ureters into the rectosigmoid, with later removal of the bladder and repair of the ventral hernia. In the male there is the added repair of the epispadias. In a series of thirty cases our results have been most gratifying. Urinary control has been exceedingly satisfactory, and there have been no deaths. Postoperative urinary infection has been slight, and in many cases, even after ten years, intravenous pyelograms show little or no kidney or ureteral infection. The technical details of the operative procedure are not pertinent for this discussion. We feel that the success of the operation depends on the multiple stage operation; transplanting each ureter through the transperitoneal route at a separate operation with a two- to three-week interval between transplants. Prevention of ascending infection is best obtained by having the anastomosis straight and unobstructed but utilizing the submucous valve action advocated by Coffey. The bladder is removed in all cases as the third stage. The psychologic problem resulting from the epispadias in the male may be of considerable moment. Our improved technique, which provides a mucous membrane-lined passage from the ejaculatory ducts plus a plastic repair of the penis itself, will, we hope, minimize this problem.

There are three types of hypospadias: glandular, penile, and perineal. The glandular type in which the urinary meatus is just at or below the sulcus usually requires no surgical treatment other than dilatation of the opening if it is so small that it may cause urinary obstruction. In the penile type the opening is on the shaft of the penis and is often associated with a forward bowing of the penis. This defect of the shaft itself usually should be repaired in the first two years of life and the plastic operation on the urethra postponed until the patient is 7 or 10 years of age. The Ombrédanne and Thiersch type of operation are the ones most favored. The perineal type of hypospadias is rare, but it is the type that most commonly gives the appearance of hermaphrodism. The urinary meatus is in the perineum. The scrotum is bifid and closely resembles the labia majora. The penis is rudimentary and resembles a hypertrophied clitoris. Great care must be exercised that the sex of the infant be correctly diagnosed. It is really a great tragedy to allow a male infant with this type of hypospadias to be named as female, and then have the mistake appreciated as late as when the child has started to school. In doubtful cases a laparotomy is justified to determine the sex. Operative care of this condition is difficult and disappointing and is best undertaken when the child is at least 10 or 12 years of age.

Undescended Testicle.—Before making any remarks on the treatment of this condition, it should be stated that a very large per cent of patients with this diagnosis do not have a true undescended testis at all but are male infants or children with a very active cremasteric reflex. A testis that has ever been seen in the scrotum or can be brought down into it is not a true undescended testicle.

Treatment with hormones has received a great deal of interest in the past ten years. From our experience with this form of therapy it is our belief that a testis that descends following the use of these extracts would probably have descended without them when puberty approached. A testis that does not descend following this treatment requires operation. Therefore we feel that this form of therapy is not only of questionable value, but that it may cause considerable damage. There is no data available now as to what the later spermatogenetic function of the testis will be in patients who have been given extended hormonal treatment before puberty. Careful observation during the first decade of life should *without hormonal therapy*

permit the physician to foretell whether or not the testis is likely to descend as puberty approaches. We prefer to wait until the boy is about 10 years of age before seriously considering orchidopexy. Notable exceptions are those cases in which there is an associated hernia that gives trouble. Here the problem is that of the hernia, and operation is dependent on this factor. The use of hormonal therapy at the Children's Hospital has been disappointing in its results, and we believe it may be dangerous as regards the spermatogenetic function in adult life.

Abstract of Discussion on Urologic Conditions in Children

Meredith F. Campbell, New York City

For facility of presentation, the diseases of the upper urinary tract in the young are here grouped as (1) anomalies, (2) tumor, (3) calculus disease, and (4) injuries, and are confined to the kidney, ureter, and adrenal. In many of these cases, complicating infection is an important consideration. In most of the cases in which the correct anatomic diagnosis is established during life, it will be made by thorough urologic study for which persistent pyuria was the indication. Since the clinical aspects of urinary infection are better appreciated by present-day pediatrists, they will be introduced here only as they complicate the lesions which form the basis of this round table discussion.

ANOMALIES OF THE KIDNEY

It is axiomatic that an anomalous organ is more prone to disease than a normal one, and for this reason these malformations are particularly important clinically and merit special diagnostic acuity.

Unilateral renal agenesis, or solitary kidney, occurs about once in 600 individuals and rarely produces symptoms unless there is associated obstruction or complicating infection. In a few instances in the past, the diseased solitary kidney has unwittingly been removed, but today adequate preoperative urographic study should prevent this tragedy. The solitary kidney is subject to all the diseases which occur when both kidneys are present, and the fundamentals of treatment are identical except that nephrectomy cannot be performed.

Renal aplasia, or hypoplasia, results from congenital failure of renal development and is characteristically unilateral, although bilateral underdevelopment has been observed. The hypoplastic organ may be only a small nubbin of sclerotic malformed renal tissue or may be half normal size. The clinical importance of the condition is identical with that of unilateral renal agenesis: The hypoplastic organ is unable to support life. Pain is the chief symptom produced by these kidneys, although when infected persistent pyuria may be the dominant manifestation. The diagnosis is made by urologic examination and nephrectomy is the treatment.

Congenital solitary renal cysts are usually unilateral and are unlikely to be clinically important unless they produce abdominal tumor or pain. The cyst wall is usually thin, and the diagnosis is made by pyelography, but the urogram may suggest malignant neoplasm. Excision of the cyst is the treatment unless the amount of parenchyma which would be left is insignificant; the last situation calls for nephrectomy.

Congenital monolocular renal cysts attract attention as they produce abdominal pain and/or a palpable mass. Large monolocular lesions may cause compression of the bowel. Nephrectomy is the treatment of choice unless a generous portion of renal parenchyma will remain following localized renal resection.

Congenital polycystic disease is almost always bilateral and is often associated with cystic disease of other organs, particularly of the liver and spleen. Pain, tumor, hematuria, and frequently pyuria are the principal symptoms; unless the renal lesion is properly identified, the clinical findings cause the diagnosis of nephritis to be made. The correct diagnosis will be established by pyelography and the

preferred treatment is that administered for nephritis. Persistent pain, hemorrhage, or infection may demand nephrectomy, but the less surgical treatment is employed, the longer the patient will live. Uremic death completes the picture.

The reduplicated, or double, kidney is the best known anomaly of renal fusion and is a part of ureteral reduplication under which we will discuss the condition.

In contralateral renal fusion, the organ from one side is fused with that of its mate. The fusion may occur across the spinal midline or one kidney may be located completely in the opposite lumbar gutter. The horseshoe type of kidney with inferior or superior polar fusion is the best known example of contralateral renal fusion. Rarely both kidneys are fused together in a mass, the so-called lump kidney. These anomalous kidneys are particularly prone to disease and in performing the complete urologic examination necessary to determine the cause of the persistent pyuria, hematuria, and pain, the malformation will be urographically demonstrated. Partial resection and removal of the diseased renal segment is the treatment when technically possible.

Congenital hydronephrosis is usually associated with congenital obstruction at the pelvic outlet and only rarely is due to faulty development of the pelvic musculature and innervation. It occurs about once in 400 individuals and produces a loin tumor and abdominal pain; persistent pyuria is the important complication. The diagnosis is made by urography and, in most instances, nephrectomy is the treatment. Yet when renal damage is minimal and the operation is technically feasible, ureteropelvoplasty should be employed. Failure of the conservative plastic operation demands secondary nephrectomy.

Anomalies of renal vascularization occur in about 15 per cent of all individuals; we are here concerned with the vessels which cross and compress the ureter. These vessels pass from the lower pole of the kidney (1) to the vena cava and/or aorta, (2) to the renal pedicle, or (3) downward to join lower abdominal or even pelvic vascular structures. Hydronephrosis is the end result of the ureteral compression; infection is the usual complication and leads to the diagnosis of chronic pyelitis. Frequently the diagnosis can be made by urography and nephrectomy will be the usual treatment, although in one-half of the cases the obstructing vessel can be divided to save the kidney.

Ureteral reduplication, or double ureter, is the most common ureteral anomaly and occurs about once in 200 individuals. In 15 per cent of the cases, the reduplication is bilateral. Adequate urologic study will often reveal that one-half of the reduplicated urinary tract is involved by infection. Frequently there is congenital stricture of the infected ureter which initially caused the urinary stasis and thus in turn predisposed to the development of the infection. In cases of mild urinary obstruction and infection above a congenital stricture in a reduplicated ureter, periodic progressive dilatation of the stricture together with urinary antisepsis, is usually curative. When the disease is more severe and is limited to one-half of the kidney and the ureter which drains it, ureteroheminephrectomy is the indicated treatment. This conservative surgical procedure preserves half of the kidney together with its normally draining ureter. When the entire kidney is diseased, ureteronephrectomy is the treatment.

In ureteral ectopy, the orifice of the ureter drains at a point other than normal; it may be lower on the trigone, in the internal sphincter, in the urethra or, in the female, in the introitus or even on the vaginal roof. Bilateral ureteral ectopy may occur. The symptoms are due to complicating renal infection or to urinary leakage from the anomalous opening. The diagnosis is made by urologic examination. If the ectopic ureter is single and the kidney above is sound, the ureter may be transplanted to a more normal site in the bladder wall (ureteroneocystostomy). If the ectopic ureter is single and the kidney is more seriously diseased, ureteronephrectomy is the treatment. Yet in most cases the ectopic ureter is one of reduplicated ureters and ureteroheminephrectomy is the indicated treatment.

Ureterocele, or intravesical cyst of the ureter, is an intracystic ballooning of the lower end of the duct and forms behind a congenitally stenosed ureteral orifice. Complicating chronic urinary infection usually causes the urologic examination to be made, at which time the lesion is cystoscopically observed. Treatment is cystoscopic division of the ureterocele to re-establish free ureterorenal urinary drainage. In some cases of large ureterocele, particularly those in which the lesion prolapses through the female urethra, a suprapubic excision of the ureterocele wall is required. In a few instances in which the ureterocele involved one of reduplicated ureters, we have performed ureteroheminephrectomy.

Congenital ureteral stricture occurs in about 0.5 per cent of all children and is the commonest obstruction of the urinary tract in the young. Hydronephrosis is the anatomic result and secondary infection is the most serious complication. This usually causes the clinical diagnosis of chronic pyelitis to be made. The diagnosis is readily established by urologic examination. The conservative treatment of ureteral stricture is periodic progressive dilatation with ureteral bougies. Yet too often the severity of the renal disease demands ureteronephrectomy. The treatment of ureteral stricture of one of reduplicated ureters has been discussed under Ureteral Reduplication.

Congenital dilatation of the upper urinary tract is associated with faulty neuromuscular development and almost always is part of the picture of neuromuscular vesical disease. The ureters and renal pelves are widely dilated and usually are secondarily infected by the time the child is submitted for urologic examination. The treatment is that of neuromuscular vesical dysfunction and is likely to be disappointing.

Occasionally ureteral kinks are observed in the young. As a rule, the ureter has become fastened by localized inflammation and the kink is firmly fixed. Renal pain due to urinary back pressure from obstruction at the point of the kink is the usual symptom, although complicating infection may cause the diagnosis of chronic pyelitis to be made. The anatomic diagnosis is readily made by urography. Treatment consists of surgical mobilization of the kink with elevation of the kidney; subsequently, urinary antisepsis and periodic progressive ureteral dilatation of the stricture at the point of kinking complete the cure.

TUMOR OF THE KIDNEY

Embryonal adenomyosarcoma (congenital mixed tumor, Wilms' tumor) is the usual renal tumor of early life and is the commonest malignant abdominal tumor in childhood. Three-fourths of these growths appear before the age of 5 years, two-thirds before the age of 3 years. They are predominantly of mesodermal origin and show a wide variety of structure, chiefly embryonal tissue. They metastasize widely through the blood stream to the spleen, liver, lungs, spine, intestines, and diaphragm, but may also directly extend locally. A mass in the loin is the chief symptom but about a fourth of the cases will have blood in the urine. The diagnosis is suggested by abdominal palpation and is confirmed by pyelography. Chief interest focuses on treatment. The average mortality in these cases when treated by surgery alone is about 95 per cent. Our greatest hope is reducing this frightful death rate lies in the correlated employment of preoperative irradiation, nephrectomy, and postoperative irradiation. Preoperatively, most of these children can be given 1,200 to 1,500 r units each through three portals (anterior-posterior, lateral, posterior-anterior) and in daily divided doses of 75 to 150 r over a period of two weeks, according to individual tolerance. It is our practice to allow two to three weeks after the cessation of irradiation before nephrectomy is carried out. At this time it will be found that the tumor has remarkably diminished in size; the operation is correspondingly less traumatic, and the immediate surgical death rate is decreased. Postoperatively

we employ irradiation in the same manner as preoperatively and include the pulmonary field. I know of two cases in which the diagnosis of Wilms' tumor seems unquestioned and apparently cured by intensive prolonged irradiation therapy, but nevertheless I strongly feel that nephrectomy should always be included in the therapeutic program. Nor am I impressed by the argument that once the diagnosis has been made, the added time required for preoperative irradiation permits the tumor to spread. As a rule these tumor cells are so highly radiosensitive that extension of the growth during the period of radiotherapy seems unlikely.

TUMORS OF THE ADRENAL

These occur about half as frequently as Wilms' tumor of the kidney. The cortical tumors are chiefly adenomatous and give rise to striking sexual changes, notably precocity. Tumors of the adrenal medulla are derived from the sympathetic nervous system and are therefore neuroganglíomas, paraganglíomas, and neurocytomas. They grow rapidly and for the greater part are highly malignant. They are not materially influenced by irradiation therapy. Most of these adrenal tumors are at first thought to be Wilms' tumor of the kidney. Pyelography and perirenal pneumography greatly assist in establishing the diagnosis. Most conditions diagnosed as retroperitoneal sarcoma in children are in truth neuroblastoma of the adrenal. Once the diagnosis has been made, adrenalectomy should be carried out. The prognosis of cortical tumors is excellent, provided the function of the opposite adrenal is adequate. The prognosis of medullary tumors is usually grave. Yet their removal offers the only hope for cure and is a chance which must be taken.

CALCULUS DISEASE

Calculus disease is comparatively much rarer in the United States than in the Orient. In older children the clinical picture resembles that observed in adults. In infancy the ureteral colic incited by the passage of uric acid crystals is likely to be misinterpreted as intestinal colic. Urinary stones are seldom recognized in children until complicating infection has occurred and a complete urologic examination is carried out. With obstruction, pain in the kidney is a prominent symptom; large stones which fill the kidney pelvis and have little or no mobility are likely to be asymptomatic or "silent." The diagnosis is made by complete urologic examination, and if the pelvic stone is large enough that its spontaneous passage seems unlikely and renal damage is not advanced, pyelotomy should be performed. With true stone pyonephrosis and widespread destruction of the kidney, employ nephrectomy.

Ureteral stones will sometimes pass following conservative dilatation of the ureter, but in children we advise against more than one such instrumental attack. If the stone is causing demonstrable obstruction and does not spontaneously pass in four weeks, open ureterotomy is strongly urged.

RENAL INJURY

Injuries of the kidney occur more often than injuries of any other part of the urinary apparatus; they result chiefly from motor vehicle and coasting accidents and falls. Simultaneous injury of other organs frequently occurs and is sometimes more important than the renal trauma. Diseased kidneys, particularly hydronephrotic organs, are more liable to injury than are the normal. The prominent symptoms of renal injury are sharp renal pain, local tenderness and the appearance of a mass in the loin with hematuria, pallor or falling blood pressure, and a diminution of circulating red cells and hemoglobin. Elevation of the white blood cell count is usually observed. As a rule, the diagnosis can be established by the history and excretory urography. Hematuria is almost always found. When excretory urography

is inconclusive, cytoscopy and retrograde pyelography should be carried out. Children with renal injuries are notoriously subject to delayed shock; following injury the patient is apparently well, up and about playing, when he suddenly falls in collapse which may be terminal.

The initial treatment should be conservative with the combat of shock by the administration of external heat, narcotics for pain, blood transfusions and intravenous infusions to restore the fluid-volume of the circulation. Hourly blood counts and blood pressure observations are imperative. Meanwhile excretory urographic studies at the bedside can usually be made. When conservative treatment fails to stop bleeding, renal exploration is demanded and should always be employed in any child who continues to show fresh hematuria longer than twenty-four hours. As a rule, nephrectomy is indicated, although in some cases of polar laceration or rupture, suture or local resection of the kidney is curative and preserves a generous segment of sound parenchyma.

DISCUSSION

QUESTION.—Will Dr. Lyttle please discuss briefly dysuria in the small child?

DR. LYTTLE.—Dysuria means difficult or painful urination. In a mild form it may be associated with an acid urine or ulcer of the meatus. When it is severe, persistent, or accompanies other symptoms, it usually means pathology in the urethra or vesical outlet. After making due allowance for overprotective parents, if the mother notices any degree of painful urination, it had better not be disregarded.

QUESTION.—In what number of cases do you find hernia associated with undescended testicle?

CHAIRMAN CAMPBELL.—In about two-thirds.

DR. LANMAN.—There is always an associated congenital hernia with an undescended testicle. In the vast majority of cases, however, this is so small as to give no symptoms. It is, however, always repaired at the time of the orchidopexy. In a fairly small proportion of cases there is a hernia large enough to give symptoms. In such cases operation for the hernia is more of a problem than the undescended testicle, and operation is done at any age that the symptoms occur and indicate operation. We feel that the age of choice for operation for undescended testicle without a hernia that causes complications is from 8 to 12 years of age.

DR. J. E. BROWN, JR., COLUMBUS, OHIO.—Do the medical men and pediatricians now concur with your ideas on hormonal therapy in cryptorchidism?

DR. LANMAN.—In general the medical men and pediatricians do agree with our views on hormonal therapy of cryptorchidism. That is, they do not use it.

DR. H. C. CLARK, NEW ROCHELLE, N. Y.—Please discuss the cause, diagnosis, and management with relation to malignancy of perineal testes.

DR. T. F. REILLY, SPRINGFIELD, MASS.—What about torsion of the cord in an undescended testicle?

CHAIRMAN CAMPBELL.—I have grouped these questions to be answered together since they are essentially concerned with the same problem. Statistical studies show that improperly descended testicles are found in about 3 per cent of all infant males but that by puberty this incidence is reduced to about 1 per cent. It is readily evident that subsequent to hormonal and growth changes about two out of three improperly descended testes will spontaneously descend during the early years of life. Yet by the administration of the anterior-pituitary-like hormone of preg-

nancy urine (I use antuitrin-S, Parke-Davis, or follutein, Lilly), we are able to anticipate, at the age of 5 or 6 years, what may be expected to occur at puberty. It is accepted by urologists that the abnormally placed testicle is not to be expected to develop normally, and the majority of these will probably be sterile. We feel that Dr. Carl Moore, of Chicago, has strikingly demonstrated that the scrotum acts as a testicular radiator: the testicle develops and matures much better in the cooler confines of the scrotum than in the abdominal cavity or inguinal canal. By the experimental placement of animal testes in the abdomen of animals and the later replacement of these organs in the scrotum, the cycle of atrophy and regeneration was demonstrated. Yet the problem of sterility in cryptorchidism in the human being can be evaluated properly only in the bilateral cases, and unfortunately to date the data is rather meager. Still we have McClellan's observations in which he studied the fertility of eighteen patients with bilateral undescended testes in whom orchidopexy had been performed in childhood at the Boston Children's Hospital. He found there was a definite fertility in 82 per cent. This is in striking contrast to the frequently stated sterility of 90 per cent in untreated bilateral cryptorchidism. On the other hand, the prognosis as to sterility should always be guarded and especially in boys with a strong tendency to eunuchoidism.

In view of these observations, we feel that the anomaly should be seriously considered before the boy is 8 years of age. In bilateral cryptorchidism, we prefer to begin treatment by the fourth year and, in unilateral cryptorchidism, by the sixth to eighth year, for shortly thereafter puberal changes begin. Moreover, there is the ever-present danger of torsion of the spermatic cord of the undescended testicle. During the past year I have seen three such instances; in two of these, the testicle was at the internal inguinal ring, and in the third, in the canal near the external inguinal ring. In the last case, the boy had unfortunately lost his right testicle by an unsuccessful operation for cryptorchidism in early childhood, and the loss of his left gland by torsion of the spermatic cord with testicular gangrene left him an eunuch.

It is my practice to advise operation when the physical examination discloses a hernia in conjunction with the cryptorchidism. In other words, the problem is patently surgical from the start. The testicle is placed in the scrotum and the hernial defect is repaired. When there is no demonstrable hernia, we feel that the boy should be given the benefit of endocrine therapy for a month to six weeks, the dose varying between 75 and 150 units of the anterior-pituitary-like hormone of pregnancy urine, given twice weekly according to the age and size of the patient. The dose will be necessarily reduced with the advent of symptoms, chiefly headache or fever. We do not believe in carrying this therapy beyond the administration of 2,500 to 3,000 rat units, and, as a rule, if the testicle is going to come down, it will do so with the administration of 1,000 rat units. We have yet to see a case in which this conservative therapy failed that operation did not disclose an anatomic reason. In most instances the testicle is found firmly bound by adhesions at the point of abnormal descent. I am aware that many pediatricians are not harmonious with my thinking, but I am decidedly adversed to the administration of large doses of the hormone for long periods of time, up to 20,000 units as advised by some. In one instance a boy had a hernia into which two fingers could be inserted, and isblateral cryptorchidism; yet over $2,000 worth of the hormone had been administered in the vain hope of correcting the anomaly. In a boy recently seen with left upper inguinal cryptorchidism and a normally placed right testis, there was advanced bilateral testicular atrophy. It is notable that he had received a large total dose of testosterone during the preceding eighteen months and we believe the testicular condition is an atrophy of disuse. The normal function of the testicle

to elaborate male sex hormone was taken over by the testosterone replacement. On the other hand, the anterior-pituitary-like hormone of pregnancy urine stimulates testicular activity.

In searching for the undescended testicle, do not neglect the perineum. As a rule, the perineal ectopic organ will produce a definite bulge. The surgical replacement of these organs in the scrotum is a relatively simple matter.

Statistical studies suggest that the incidence of testicular neoplasm is slightly higher in the imperfectly descended organ, but we do not advance this phase of the anomaly as the sole indication for operation. Surgical therapy is advised as a procedure which will encourage maximal testicular development, and function will prevent torsion of the cord of the improperly descended gland.

DR. W. C. A. STEFFEN, FLUSHING, N. Y.—What is the normal blood pressure range at 4, 8, and 12 years of age?

DR. LYTTLE.—The systolic blood pressure at 4 years of age should normally be under 100 mm. Hg. At 8 and 12 years it should be under 110 mm. Hg. In both sexes at or just before puberty a transient elevation in blood pressure is frequently observed. Casual determinations of blood pressure in children are not always informative. For accurate information repeated observations must be made.

DR. W. L. CRAWFORD, ROCKFORD, ILL.—Will you please discuss the question of whether radiation is purposely withheld until after surgery in Wilms' tumor?

CHAIRMAN CAMPBELL.—We employ both preoperative and postoperative irradiation but strongly feel that the preoperative radiotherapy is by far the more important. (Dr. Lanman will state the contrary view.) We firmly believe that preoperative irradiation carried out over a period of ten to twenty days does not notably lessen the child's chances and certainly the striking tumor shrinkage which customarily occurs materially reduces nephrectomy shock.

DR. LANMAN.—The experience with a series of sixty cases of Wilms' tumor at the Boston Children's Hospital has led us to the firm belief that preoperative radiation is undesirable. We know of no proved case of Wilms' tumor that has been cured by radiation alone. We admit that this tumor is radiosensitive but feel that it is impossible to differentiate accurately before operation between Wilms' tumor and the nonradiosensitive neuroblastoma of the kidney region. Preoperative radiation wastes times, and in a tumor of this sort it is impossible to foretell just when metastases by the blood stream will take place. We have some interesting photomicrographs of tumor cells actually free in the tributaries of the renal vein in a specimen of Wilms' tumor removed at operation. Preoperative radiation was advocated largely to make the tumor smaller and so make the technical difficulties of its operative removal less and so to decrease operative mortality. Our operative mortality in the last ten years is only 3 per cent, and we have had no operative deaths since 1933.

More significant, however, is the fact that in our series there are now sixteen known cured patients. We have been able to find reported in the literature only twenty-six other cured patients. Only nine of these had preoperative radiation. Only one of our sixteen cured patients had preoperative radiation. While we cannot prove it, we suspect that preoperative radiation may permit an easier dissemination into the blood stream of the tumor cells. Our operative mortality has been improved by better understanding of pre- and postoperative care. In particular we feel it of importance to attack all these tumors through a transperitoneal incision and to ligate the renal vessels before there has been any attempt to free the tumor itself. This approach permits a minimal handling of the tumor, and we feel that it

is desirable that these tumors be palpated and manipulated as little as possible before removal in order to prevent the possibility of setting free in the blood stream some of the tumor cells.

The size of the tumor has no relation to the prognosis.

DR. CLARK.—What is the best age to train a male; female?

DR. LYTTLE.—Some mothers say it is easier to train a female child than a male. For all practical purposes it seems best to begin training for bladder control when the child begins to walk.

DR. M. H. BASS, NEW YORK, N. Y.—What has the relation of the size of Wilms' tumor to do with the prognosis of the life of the patient?

CHAIRMAN CAMPBELL.—Absolutely none. It is a matter of metastatic spread. Dr. Murray Bass cited a child with an extremely small primary Wilms' tumor who rapidly died of widespread metastases. Yet simultaneous with this, another child with an enormous Wilms' tumor was apparently cured by nephrectomy. In general, the longer the tumor has persisted, the greater is the likelihood of metastases. Once the tumor is outside the kidney, the chance of cure may be considered essentially nil.

DR. W. S. ANDERSON, WASHINGTON, D. C.—Is it the opinion of the other two discussion leaders that one attack of pyuria in females associated with acute pharyngitis requires intravenous pyelography?

DR. LANMAN AND DR. CAMPBELL.—It certainly is worth while thinking about this very seriously.

DR. CRAWFORD.—Will you discuss the length of time needed for adequate drainage after dilating a ureterovesical junction stricture?

CHAIRMAN CAMPBELL.—This is a highly variable and individualistic thing. These congenital strictures must be periodically progressively dilated, and the stricture remains cured only when it remains dilated. We strongly feel that even though therapeutic success has apparently been obtained by this conservative method, the child should still have periodic examinations at intervals of one to two years to make certain that recontraction of the stricture has not occurred, that no renal damage is in progress, and that the urine is sterile.

DR. BROWN.—Please discuss briefly chemotherapy: (a) choice of drug; (b) dosage; (c) how long you continue drug; (d) value of alkalinization.

CHAIRMAN CAMPBELL.—While I am aware that the sulfonamide drugs are the first choice with most pediatricians and probably with most urologists, it is my usual practice to try the mandelic acid preparations first, particularly with the child who is to be treated as an ambulatory patient and not under close daily medical supervision.

Several mandelic acid compounds are on the market, including the syrup and elixir of mandelic acid, calcium mandelate, ammonium mandelate. Recently I have been using a preparation called mandelamine. The dose varies from 2 to 10 Gm. in twenty-four hours, according to the size and age of the child. A few patients will develop a mandelic acid intolerance, manifested chiefly by gastrointestinal upsets. Occasionally there is mild hematuria, and with this the medication is changed to a sulfonamide drug.

Of the sulfonamides, I prefer sulfathiazole, using doses of 10 to 30 gr. a day, according to the age and size of the child. Yet it is important that the child be watched closely during the period the medication is being taken, particularly from

a hemopoietic standpoint. Gastrointestinal disturbances and fever are not uncommon reactions, and when it is demonstrated that the child is sensitive to the drug, a change to mandelic acid is made.

The period of drug administration should not be longer than seven to eight days in children, and following its cessation and after a wait of three to four days, a catheterized specimen is taken for gram stain or, preferably, culture. If the culture is sterile, a recheck culture is made in another week or ten days. If the culture still shows infection, the medication is repeated in slightly larger doses or a switch to another antiseptic is made. It is notable that if the urine can be sterilized by methenamine therapy alone, it may be accepted that no important stasis-producing condition exists in the urinary tract.

Alkalinization is valuable only as it assists in the combat of acidosis in acutely ill patients, or as it serves to allay local irritability in acute vesical inflammation when the urine is highly acid. The periodic switching of the urine reaction is antiquated empiricism and of no value.

DR. J. B. BILDERBACK, PORTLAND, ORE.—Do you have difficulty due to abdominal distention in getting good plates in intravenous pyelography in small children?

DR. G. C. MALLEY, ZANESVILLE, OHIO.—Outline preparation (enema, dehydration, etc.) for intravenous pyelogram.

DR. LANMAN.—Intravenous pyelography in children is most satisfactory and informative. We experience no great difficulty in getting into the veins, even in small infants, and in these small patients we use the veins in the back of the hand, on the scalp, or about the ankle. We do not use the dye subcutaneously.

We have found that much more satisfactory plates are obtained if we have not had an elaborate preparation. It is much better to have the patient up and about with the usual breakfast, and we give no cathartic the night before. We do, however, limit the fluids from midnight on, unless there is a contraindication to so doing. We feel that if the specific gravity of urine is much below 1020 or 1018, the concentration of the dye in the excreted urine will not give a satisfactory plate. It is important to determine how much the patient can concentrate the urine before considering intravenous pyelography. The chief difficulty encountered in small children is gas in the stomach and bowel, and if the child is fussy and crying, there is apt to be a considerable amount of air swallowed and therefore such procedures as frighten or disturb the child are not done. A scout film is always taken before the dye is injected, and if there is excessive amount of gas, it may often be well to postpone the procedure.

DR. STEFFEN.—Can you differentiate between a neuroblastoma and Wilms' tumor before operation?

CHAIRMAN CAMPBELL.—As a rule, there is no accurate method. In two cases we applied the irradiation test. Most Wilms' tumors are exceedingly radiosensitive and rapidly decrease in size, while the neuroblastomas show essentially no response. In both of these cases there was no response, so we assumed a neuroblastoma existed and operation confirmed this. A large mass in the renal region and a pyelogram which shows the renal pelvis pushed far downward and obviously compressed from above is suggestive of an adrenal tumor. Yet a large Wilms' tumor involving the upper portion of the kidney will give the same clinical and urographic evidence.

QUESTION.—When do you operate on hypospadias?

DR. CAMPBELL.—I prefer to do the first-stage operation by the end of the first year. In carrying out this procedure, the hypoplastic fibrous corpus spongiosum is excised from the region of the natural external meatal opening at the glans penis as far backward as it can be identified and always some distance proximal to the hypospadiac meatus. This corrects the congenital (chordee) deformity by removing the G-string effect and permits the penis to grow more normal and straight. The successive stages of the operation in which the plastic creation of a new urethra is accomplished are carried out when the child is 4, 5, or 6 years of age, and in any event, not until the external genitalia are large enough to provide adequate tissue for the reconstruction. In some cases, we have waited until the child was 8 or 10 years of age. Yet by this time many of these boys are extremely genital-conscious and the psychologic aspects of the anomaly merit serious consideration. In most cases I employ the Ombrédanne operation, and in pseudovaginal hypospadias with the meatus abnormally placed in front of the rectum, a three- or four-stage operation is frequently necessary before the canal empties normally at the glans.

DR. CHARLES SNELLING, TORONTO, CAN.—What is the characteristic picture shown in the pyelogram when the stone is not radiopaque?

CHAIRMAN CAMPBELL.—It stands out as a vacuole which we commonly designate as a "negative" shadow.

DR. H. P. FINE, PERTH AMBOY, N. J.—In traumatic orchitis followed by an atrophic testicle is any hormonal therapy indicated or useful?

CHAIRMAN CAMPBELL.—No. In bilateral post-traumatic testicular atrophy, the administration of testosterone for its replacement value is rational therapy but should not be required in unilateral testicular atrophy when one good testicle remains.

DR. CHARLES BRADLEY, E. PROVIDENCE, R. I.—Please discuss technique and reliability of findings in the urethrogram.

CHAIRMAN CAMPBELL.—Several apparatuses have been devised for carrying out this procedure in adults but they are impracticable to use in children. I simply take a half-ounce blunt-nosed urethral syringe and, grasping the glans penis rather firmly, make the urethral injection of 5, 10, or 15 c.c. of 40 per cent diodrast solution, stopping the injection if the child complains of pain. The radiographic exposures are then made in the nearly oblique angle with the underthigh flexed high and the upper thigh extended backward. By this method we have beautifully demonstrated urethral strictures, urethral diverticula, and other abnormalities of urethral caliber.

QUESTION.—In the case of double ureters with no demonstrable change in the pyelogram and in which the urine clears with chemotherapy and stays clear, do you do anything?

CHAIRMAN CAMPBELL.—No. Before considering the child cured of the infection, however, I insist upon at least two negative cultures of aseptically collected urine specimens. If this test of cure is insisted upon, recurrence of so-called "pyelitis" will be infinitely reduced.

DR. J. R. BOWMAN, JOHNSON CITY, TENN.—Do you have difficulty in getting good urographic films in small children with abdominal distention?

CHAIRMAN CAMPBELL.—Yes. We consider an average of 50 per cent of satisfactory films a good result. Yet despite unsatisfactory findings in such a large number of children, we feel the method is always worth employing, particu-

larly preliminary to cystoscopic and instrumental investigation. The compression of the lower ureters by a rubber ball held tightly against the suprapubic area or an inflated rubber bag in the upper rectum will materially improve the urographic details in the upper urinary tract. These methods can be satisfactorily used in cooperative children.

QUESTION.—How do you prepare patients for urograms?

CHAIRMAN CAMPBELL.—I prefer to take them off the street as it were. The less the patient is subjected to dehydration, catharsis, enemas, and abstinence from food, the less will be the intestinal distention. For a time we employed small injections of prostigmine and found that about five minutes after the injection there was a copious discharge of intestinal gas and excellent urograms were obtainable. Yet, a pharmacologic study we made of the normal urinary tract in children showed a similar contractural stimulation effect on the ureters and renal pelvis; in some cases the capacity of the renal pelvis was reduced to a third of the normal. For these reasons we have discontinued the use of intestinal-stimulating drugs, such as prostigmine and pitressin. It is especially important that the child should not miss a meal prior to the performance of the radiographic examination, as this encourages intestinal distention.

DR. A. G. DAVIS, UTICA, N. Y.—How do you use dyes subcutaneously for kidney investigation when unable to get into the vein?

CHAIRMAN CAMPBELL.—I have used this method but twice and rapidly discarded it as unnecessarily tedious. There is no reason why one should not be able to make the intravenous injection even in the smallest infant in whom we use the fontanel or commonly the external jugular. In slightly older children, the veins of the wrist or back of the hand or of the foot are usually available. We are seldom able to make a median vein injection in children under 2 years of age.

DR. BRADLEY.—Please discuss the technique of air injection into the perirenal space for the demonstration of the adrenal.

CHAIRMAN CAMPBELL.—Having sterilized the skin with iodine, mercurochrome, or alcohol, and having infiltrated the proposed path of the injection needle with a small amount of 1 per cent novocaine, the needle through which the air injection is made is inserted about 1.5 cm. below the border of the last rib and about 3 cm. from the spinal midline. In older children the injection is made slightly more lateral. The injecting needle (we use a 20 or 22 F. needle about 2½ inches long) is introduced and when the innermost fascial plane has been penetrated, aspiration is employed to make sure the needle is not in a vessel. If not, a test injection is made. For this injection in children, we customarily use a 100 c.c. glass syringe, and on the average introduce 75 to 150 c.c. of air, according to the size of the child. Radiographic exposures are made four hours, eight hours, and twenty-four hours following the injection. In a certain number of cases it will be found that the air has been injected intraperitoneally and in two of our cases the injection was made directly into the bowel. Yet, no untoward results followed. The notable paucity of perirenal fat in children greatly increases the technical difficulties of the procedure. When this method has been properly employed, not only will the kidney stand out in bold relief, but as a rule the outline of the adrenal gland will be satisfactorily demonstrated.

News and Notes

Dr. Maynard Ladd died March 9 at the Media Pennsylvania Hospital after a long illness. He was 69 years of age. Dr. Ladd practiced pediatrics at Boston for many years and taught at the Harvard Medical School where he was an Associate in Pediatrics. At the time of his retirement in 1936 he was consulting physician to the Children's Hospital and director of the Preventive Clinic. He served as Chief of the Children's Bureau of the American Red Cross in France from 1917 to 1919 and was decorated by the French government. He was an emeritus fellow of the Academy of Pediatrics and an emeritus member of the American Pediatric Society, of which he was president in 1922.

Book Reviews

Communicable Disease Nursing. Theresa A. Lynch, R.N., St. Louis, 1942, The C. V. Mosby Co. Pp. 675. Price $3.75.

The author, who was formerly Superintendent of Nurses and Director of Instruction at the Willard Parker Hospital, and at present is an instructor in Education at New York University, is unusually well qualified by her experience and training to write a text on communicable disease nursing. The first part of the book contains a discussion of certain general matters, as prevention and medical asepsis. In Part II the detailed nursing and care of specific communicable diseases is considered. For each disease there is a brief discussion of such matters as etiology, pathology, transmission, and treatment, followed by a more extensive discussion of the nursing care. Part V contains a chapter on the home nursing care of communicable diseases. An extensive appendix contains such items as the New York State Department of Health rules and regulations for the handling of communicable disease and a discussion of home nursing procedures. One of the most valuable parts of the text is the thoroughness with which it has been illustrated. The serial illustrations of the handling of gowns are worth many pages of text description. The textual matter relating to the specific disease is as accurate as such summaries can be and as much as any nurse should need to know.

Abdominal Surgery of Infancy and Childhood. William E. Ladd, M.D., F.A.C.S., and Robert E. Gross, M.D., Philadelphia, 1941, W. B. Saunders Co. Pp. 455. Price $10.00.

The reviewer has been on the surgical staff of a children's hospital, with university affiliations, in a large metropolitan area for many years. He has therefore had an opportunity, like the authors, to study surgical problems in children, with the help of many other clinical and laboratory groups. He feels that this book, developed in such an atmosphere and obviously not a compilation but a record of personal experiences, will be of the greatest help to the general surgeon. It emphasizes certain conditions which occur only in childhood and are usually glossed over in the average text on general surgery. It is limited to abdominal conditions, but it is here that surgical problems are met in children which are not seen in adults. Every important abdominal condition is adequately covered and the treatment outlined. The

arrangement of the material, the clear exposition limited only to essential facts, and the excellent illustrations make this book a real aid to anyone doing surgery. It is the sort of help we have been waiting for, and it will doubtless meet with well-deserved popularity. The publishers are to be commended for a beautiful piece of workmanship.

Erratum

In the February issue of the JOURNAL in the article, "The Etiology of Acute Infectious Gingivostomatitis (Vincent's Stomatitis)," by William C. Black, p. 159, acknowledgment was made to part of the expenses of the investigation being defrayed by funds from the Michael O'Connell Foundation. This work was financed by funds from the Rees-Stealy Medical Research Foundation.